VOLUME 44 NUMBER 1

ARCHIVES OF

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JULY 1950

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $12.00

Entered as Second Class Matter Feb. 7, 1929, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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BASE CURVES AND OCULAR IMAGE ASYMMETRY

The correct choice of the curves necessary to produce a given ophthalmic lens is important. Modern corrected curve lenses are based on the curves of Tschering, which curves free the lenses from the astigmatism of oblique pencils and result in markedly improved marginal vision.

In this mechanized age, clear marginal vision is a safety factor, and corrected curves result in much better patient comfort and efficiency.

Correct base curves are also very important because they can change the size of the retinal images. The size of the retinal image depends on the correction, of course, but also on the distance from the nodal or principal point of the eye to the nodal point of the lens. In a plus lens as this distance increases the image size becomes larger and in a minus lens the image size becomes smaller.

The position of the nodal point of any ophthalmic lens depends upon its curvature. It is upon this fact that the lenses to correct unequal retinal images are based (Scientific Corner, December 1942).

The above facts are presented because they have a bearing on the case of Mr. S. which we present now. Mr. S. required a + 1.50 sphere in each eye combined with a small cylinder. The correction had been worn comfortably for years. One lens was broken and replaced and Mr. S. immediately started having eye trouble.

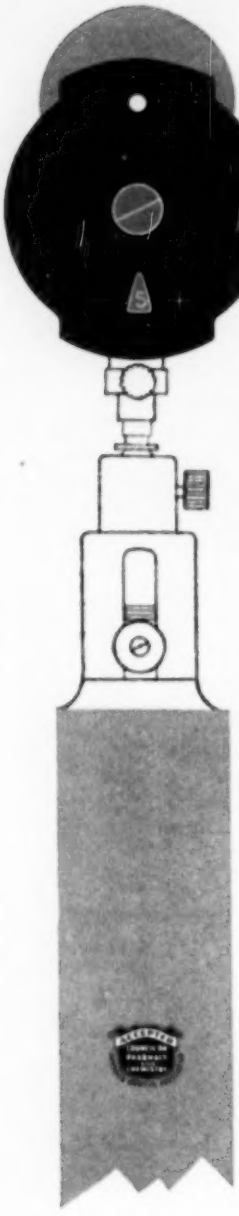
He reported back to his oculist who checked the new lens for power, axis, position of the optical centers, etc., and found everything as it should be. The oculist then checked the base curve of the new lens and found it very different from the curve of the old lens. A new lens was ordered with the same base curve as the old lens and the patient's symptoms disappeared.

We think this case interesting because with unmatched base curves, the patient reported the most common symptoms of ocular image asymmetry: inability to read or do close work comfortably, discomfort at movies and headaches.

The amount of ocular image asymmetry induced in this case was small—less than one per cent. But very important because it resulted in unwearable glasses.

So many cases of this type have come to our attention that we present this one with the hope that it may not only solve an immediate problem but will also result in more control by the oculist of his patient's lens replacements.

"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"



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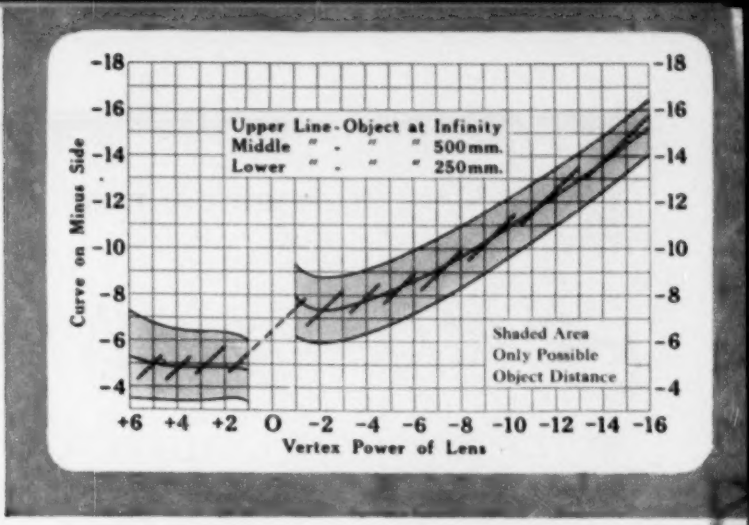

This chart shows the *best curves* for minus sides of sphere powers and the diagonal lines indicate the position of the base curves of the new series.

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The History of the Guild

THE NATIONAL GUILD IS FOUNDED

The Philadelphia Guild of Prescription Opticians, founded in 1923, had hardly begun functioning before inquiries came from out-of-town opticians: "What is the Guild?"; "What does it do?"

The practical answer was to invite the inquiring dispenser to attend a meeting of the Philadelphia Guild, to find out personally.

And having attended the meeting, almost always the response was the same: "The things you discuss are the things *I* want to discuss. The things you are doing are the things *I* want to do. Isn't there some way in which *I* can join?"

But how could a man from New York, New Jersey, Delaware, Massachusetts or Connecticut become a member of a *Philadelphia* Guild?

There was only one answer, and that was the formation of a *national* organization, which took place in 1925 when the Guild of Prescription Opticians of America was formed.

The first year there were only 17 members. This Silver Anniversary year the Guild's membership is nearing 350; from the west coast to the eastern seaboard, from Canada to Florida.

There were *reasons* for this growth; reasons that we shall tell you about in later chapters of this little "history".

The Guild of Prescription Opticians of America, Inc.
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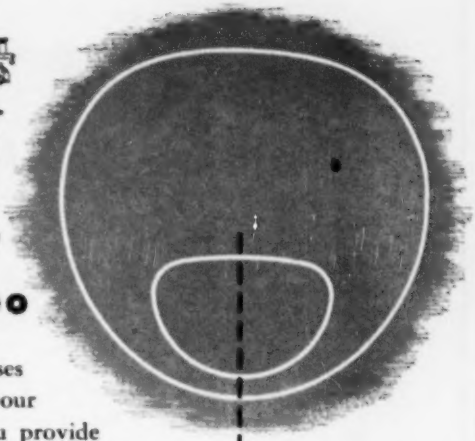

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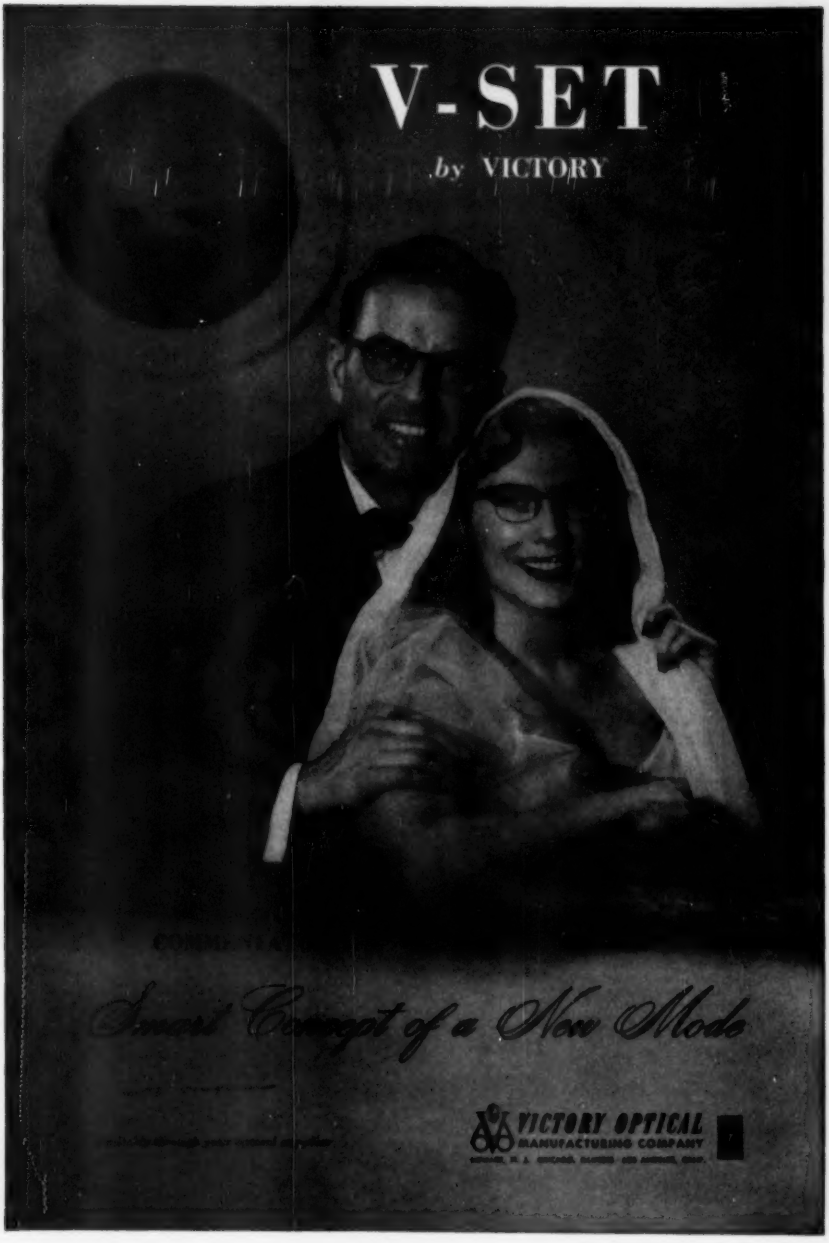
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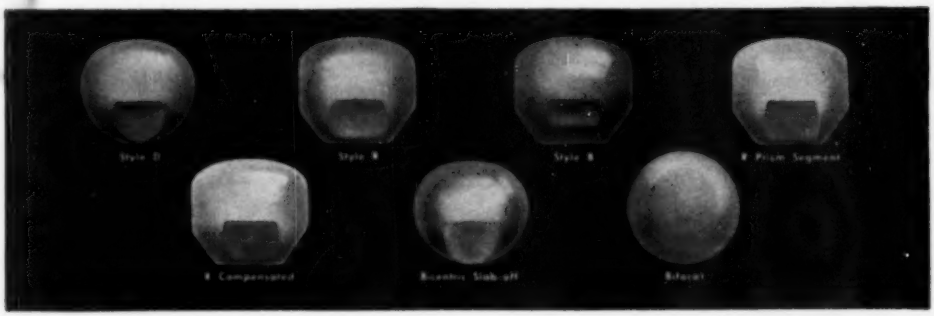

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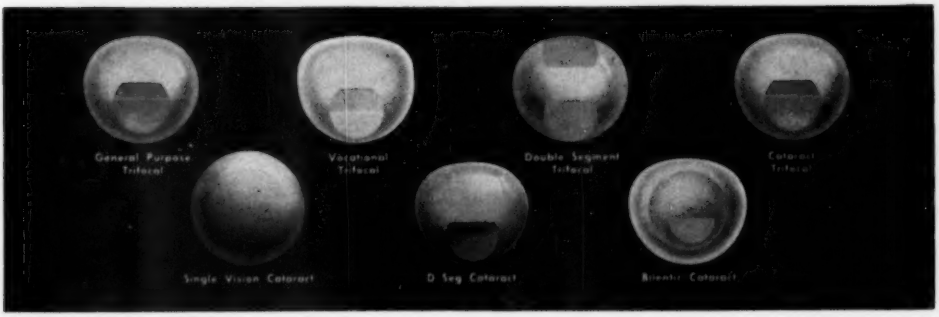

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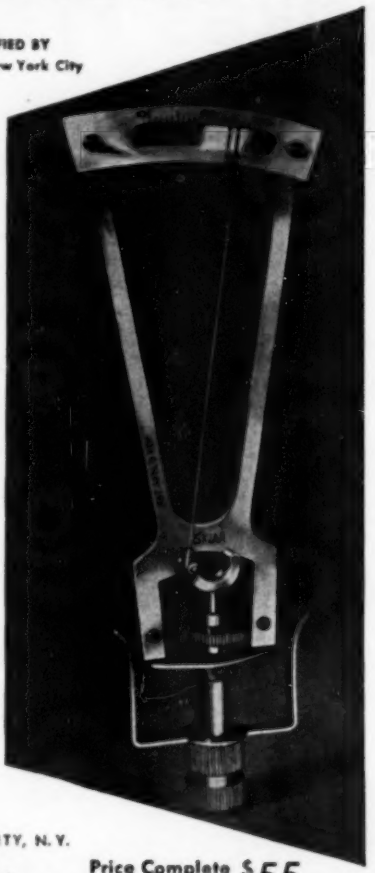

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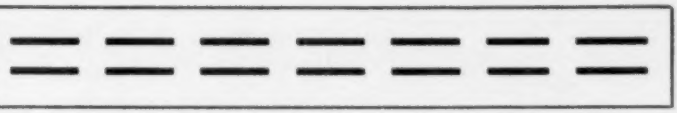

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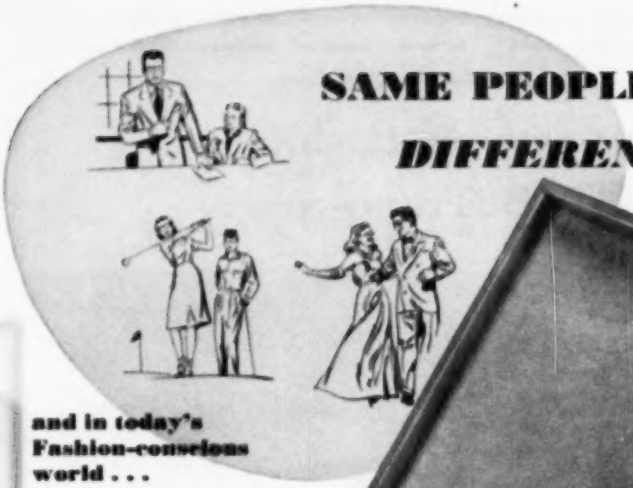

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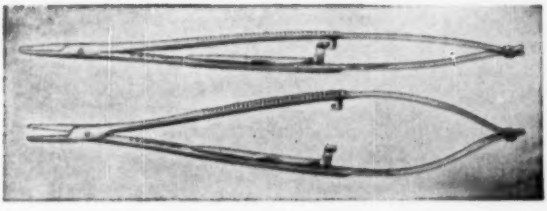

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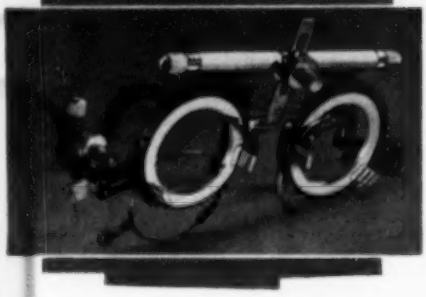

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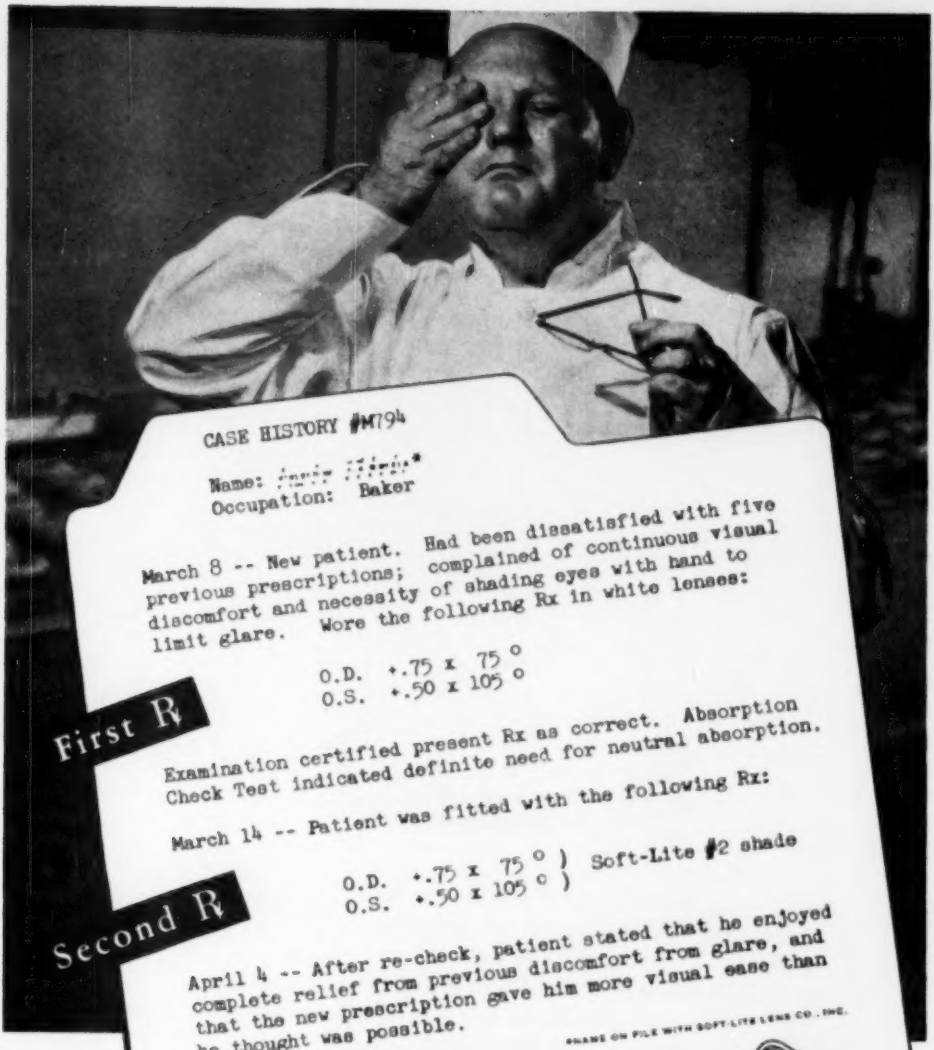

CASE HISTORY #M794

Name: [illegible]*
Occupation: Baker

March 8 -- New patient. Had been dissatisfied with five previous prescriptions; complained of continuous visual discomfort and necessity of shading eyes with hand to limit glare. Wore the following Rx in white lenses:

First Rx

O.D. +.75 x 75 °
O.S. +.50 x 105 °

Examination certified present Rx as correct. Absorption Check Test indicated definite need for neutral absorption.

March 14 -- Patient was fitted with the following Rx:

Second Rx

O.D. +.75 x 75 °) Soft-Lite #2 shade
O.S. +.50 x 105 °)

April 4 -- After re-check, patient stated that he enjoyed complete relief from previous discomfort from glare, and that the new prescription gave him more visual ease than he thought was possible.

*NAME ON FILE WITH SOFT-LITE LENS CO., INC.

another case history that proves

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Soft-Lite Lenses: Featured in Orthogon and Panoptik

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ARCHIVES OF OPHTHALMOLOGY

VOLUME 44 JULY 1950 NUMBER 1

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RECONSTRUCTION OF THE FLOOR OF THE ORBIT BY BONE GRAFTS

JOHN MARQUIS CONVERSE, M.D.
AND
BYRON SMITH, M.D.
NEW YORK

THE ORBITAL contour may be distorted by comminution of bone and telescoping of fragments in maxillary and zygomatic fractures, congenital malformations, loss of bone from osteomyelitis, radiation necrosis and destructive surgical procedures necessary in the eradication of malignant disease. Such distortion or disorganization points to the need for a suitable technic for restoration of the orbital floor and replacement of missing bone.

In the case of comminution of bone along the infraorbital rim and in the orbital floor the fragments may sink into the maxillary sinus. Contraction occurs during the healing of the torn mucosa of the maxillary sinus, and the scar tissue formed tends further to draw the comminuted fragments downward. When fracture of the zygomatic bone results in separation of the frontozygomatic junction, ptosis of the eyeball is particularly evident (fig. 1*a*). The lateral palpebral ligament and the thick portion of Tenon's capsule, known as the suspensory ligament of the eyeball, are inserted into the orbital process of the zygomatic bone. A downward displacement of the bone causes a similar derangement of these insertions, with consequent ptosis of the eyeball, accompanied with a downward migration of the lateral canthus (fig. 1*b* to *e*).

Diplopia following fractures of the zygomatic bone requires careful evaluation of the deformity and examination to determine the possible presence of a frontozygomatic separation. Early treatment entails packing the maxillary sinus through an opening in the canine fossa and elevating the fractured zygomatic bone. Direct interosseous wiring of the zygoma to the frontal bone at the point of separation is an occasional requirement. The early treatment of such conditions in order to prevent

Read before the New York Academy of Medicine, Section of Ophthalmology, Nov. 21, 1949.

From the Plastic Surgery Clinic, Manhattan Eye, Ear and Throat Hospital, and the Plastic Surgery Unit, Department of Surgery, New York University-Bellevue Medical Center.

further complications has been stressed in a recent textbook by Kazanjian and Converse.[1]

Osteomyelitis and malignant disease have been responsible for loss of bone varying in extent from small sections of the orbital margin to loss of the entire floor. Such conditions may be associated with extensive loss of the maxilla and zygomatic bone. Extreme ptosis of the eyeball is present when the entire floor of the orbit is missing. Disorganization and loss of bone may result not only in deformity but also in functional disturbances.

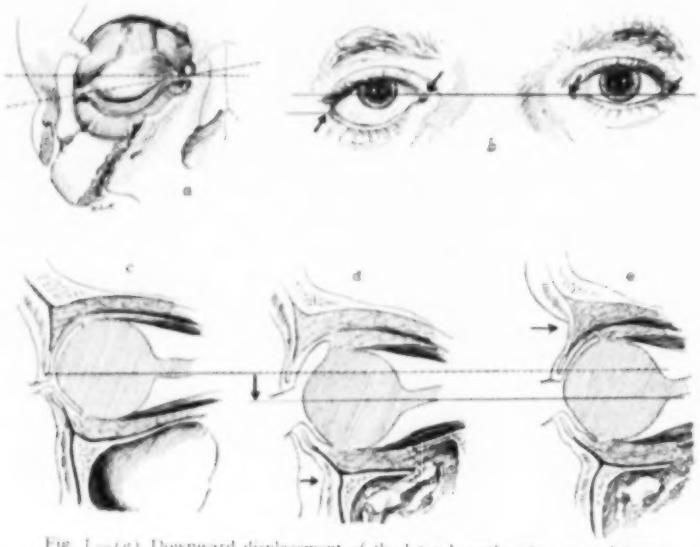

Fig. 1.—(*a*) Downward displacement of the lateral canthus in cases of fronto-zygomatic separation; (*b*) degree of downward displacement of the right lateral canthus as measured by the ruler test; (*c*) normal anatomic relation of the orbit to the orbital contents; (*d*) downward displacement of the orbital contents, caused by depression of the floor of the orbit. The lower lid is retracted because the septum orbitale is pulled backward by scar tissue. (*e*) Deepening of the superior palpebral sulcus due to ptosis of the globe.

DEFORMITY

Absence of infraorbital margin results in depression and a posterior and downward pull of the lower lid; when the entire floor has been resected, the characteristic deformity seen in figure 2 is present. Deepening of the superior palpebral fold is indicative of the ptosis of the

1. Kazanjian, V. H., and Converse, J. M.: The Surgical Treatment of Facial Injuries, Baltimore, Williams & Wilkins Company, 1949.

eyeball. Occasionally one may note the outline of the levator muscle beneath the skin. Recession of the insertion of the septum orbitale causes the lower lid to be drawn backward and downward. Although this deformity is caused by a shortening of the septum orbitale, the condition has been attributed to loss of skin of the lid or to atrophy of the lower lid. Cases have been observed in which inadvertent skin grafting has had no beneficial effect. The tendency to shortening of the inferior rectus muscle and to downward rotation of the eyeball may be pronounced in some cases (fig. 3).

The extent of ptosis of the orbital contents may be estimated by the ruler test (fig. 1*b*). Loss of the orbital margin causes the eyeball to appear prominent (pseudoexophthalmos), owing to an increase in the vertical width of the interpalpebral fissure. This condition is readily

Fig. 2 (case 1).—Reconstruction of the maxilla, zygomatic bone and floor of the orbit by bone grafts.

A, deformity resulting from resection of the maxilla and zygomatic bone for carcinoma of the left maxillary sinus. Note the ptosis of the contents of the left orbit, deepening of the superior palpebral sulcus and retraction of the lower lid, as illustrated in *c* to *e* of figure 1.

B, appearance of patient after surgical reconstruction by bone grafts.

analyzed by comparative measurements of the height of the interpalpebral distance (*1*) with the eyes in the primary position, (*2*) with the gaze elevated and (*3*) with the eye in the position of depression.

FUNCTIONAL DISTURBANCES

Minor loss of bone of the infraorbital margin, resulting in slight deformity, may cause little functional disturbance. In cases of greater loss of bone, diplopia is the most distressing consequence of ptosis of the eyeball. Of our series of 14 cases, diplopia was present in 3. Correction of diplopia by reconstruction of the floor of the orbit with bone grafts,

using a technic previously employed by Sir Harold Gillies, was reported by one of us (Converse[2]). Other ocular disturbances than diplopia may be present. Muscular imbalance may be caused by downward displacement or the orbital contents, misdirection of the pull of the

Fig. 3.—Deformity caused by loss of the floor of the orbit from radiation necrosis. Note rotation of the globe caused by scar contracture of the inferior rectus muscle.

extraocular muscles or injury to the oculorotary nerve supply and structural changes in the involved muscles.

2. Converse, J. M.: Two Plastic Operations for Repair of the Orbit Following Severe Trauma and Extensive Comminuted Fracture, Arch. Ophth. **31**:323 (April) 1944.

The patient may not recognize diplopia early if the eye is temporarily closed by edema of the lids, or by dressings or because of intraocular injury. The resulting injury is not characteristic. Each case is an individual one, and repeated diagnostic studies of the muscles of the eye are necessary before and after bone surgery.

Other functional disturbances noted in our series of cases include sensory disturbances along the cutaneous distribution of the supraorbital or the infraorbital nerves. In 1 case hypesthesia of the cornea on the injured side pointed to the possibility of neuroparalytic keratitis. Normal levator function with paralysis of the homolateral half of the frontalis muscle, culminating in malposition of the eyebrow, was observed in 3 cases. This complication is a fairly common result if soft tissue wounds intercept the nerve supply to the frontalis muscle. Fractures extending to the apex of the orbit through the optic canal, trauma resulting in intrathecal hemorrhage or damage to the optic nerve usually causes a decrease of visual function or initiates atrophy of the optic nerve.

Dacryocystitis, secondary to obstruction of the nasolacrimal duct, is an occasional complication and indicates delay in surgical reconstruction of the orbital floor. Good surgical results cannot be expected until infection of the lacrimal tract has been eliminated. Probing the nasolacrimal duct may be a useful diagnostic aid. Dacryocystography with iodized oil U.S.P. or other opaque medium and the elimination of nasal obstruction and sinusal infection should precede the surgical plan for dacryocystorhinostomy. In 2 such cases in our series the sac was sutured to nasal mucosal flaps through an intraosseous window into the nasal cavity.

Fractures of the orbital walls are commonly accompanied with enophthalmos. Increase in the vertical width of the affected interpalpebral fissure may give the impression of exophthalmos. Determination of the degree of exophthalmos or enophthalmos is based on the relative position of a projected line from the lateral orbital margin to the profile of the zenith of the cornea. In the presence of loss of bone and osseous malposition, fixed points on the affected and unaffected sides cannot be used in diagnosis. In such cases the determination of the degree of ocular protrusion or recession is measured by the difference in the number of millimeters required to focus an instrument on each cornea, with the patient's head and the focusing instrument placed in a central position. This measurement may be calculated with a corneal microscope and head rest or by means of an adapted keratometer. The calibration of either instrument for use as an exophthalmometer is not a difficult procedure. In our experience, the complete or partial correction of enophthalmos may be best observed after restoration of the orbital contents by bone grafts. The operation has also been successful for restoration of normal contour of the supratarsal sulcus.

ROENTGENOGRAPHIC STUDIES

Additional information on the condition of the orbit may be obtained from a roentgenographic examination (Pfeiffer[3]) which employs five projections: the Caldwell view, the Waters view, the lateral view, the view of the optic canals and the basal view.

The Caldwell view, taken in the nose-forehead position, defines the frontal projection of the orbits and superimposes the outline of the petrous portions of the temporal bones on the superior maxillas. The orbital margins, superior orbital fissures, sphenoidal ridges and lines of the temporal fossae are visualized in the roentgenogram. The frontal and ethmoidal sinuses and the nasal fossae are also clearly defined.

The Waters view, taken in the nose-chin position, projects the superior maxilla without superimposition of the petrous bones. In such a view the maxillary sinuses are clearly defined. The orbits, shown above the maxillary sinuses, are distorted, owing to the inclined position. In the Waters view the orbital boundaries are clearly indicated, as are the zygomatic bones and the arches.

The lateral view is advantageous for the proper interpretation of anterior and posterior relations.

Clearly defined views of the optic canals can be obtained only by projection of the optic canals.

Technical difficulties in obtaining the basal view require the elevation of the patient's body above the level of the x-ray table to compensate for the limited extensibility of the cervical portion of the spine. The basal view is used primarily to obtain details of the middle cranial fossa, the sella turcica and the comparative symmetry of the orbits and fossae.

Stereoscopic roentgenograms of both orbits, properly centered for comparison, are an adjunct in detailed analysis. Proper positioning to obtain symmetric projection is necessary for correct exposure and interpretation.

RECONSTRUCTIVE SURGERY

When there is a frontozygomatic separation, restoration of contour of the lateral wall of the orbit should be assured by loosening the displaced zygomatic bone from its malunited position and immobilizing it to the frontal bone by direct interosseous wiring. When bone has been lost through sequestration or radical surgical measures, or when the bone is so finely comminuted that it cannot be replaced, restoration of the orbital floor by bone grafts is the method of choice. After the restoration of bone contour, subsequent procedures may include surgical correction of the extraocular muscles and lids. At least six months should elapse after bone surgery before surgical measures on the

3. Pfeiffer, R. L.: Roentgenography of Exophthalmos, with Notes on the Roentgen Ray in Ophthalmology, Tr. Am. Ophth. Soc. **39**:492, 1941.

oculorotary structures are contemplated. Provided that nerve injury is a factor in the heterotropia, at least one year from the time of injury should be allowed for spontaneous nerve regeneration before compensation by extraocular muscle surgery is planned. Corrective lid-supporting surgical therapy is the final procedure if blepharoptosis complicates the picture.

The correction of interpalpebral widening is deferred until the bone graft has solidified and lymphatic channels and circulation are reestablished. The period of such tissue adjustment is considered to be not less than eight weeks. The surgical correction of interpalpebral widening by lateral tarsorrhaphy eliminates the staring appearance and pseudoexophthalmos.

Various types of implants have been utilized to restore the continuity of the orbital floor and to raise the depressed contents. Judging from our experience and from recent reports (DeVoe [4]; White [5]), implants of foreign substances (vitallium,[6] tantalum, acrylic resins, glass wool) tend to become extruded. Preserved cartilage homografts are slowly invaded by fibrous tissue and absorbed; autogenous cartilage remains intact but has a tendency to curl. Bone presents a number of advantages: It becomes consolidated with the adjacent bone provided that the graft is placed in contact with healthy bone stripped of its periosteum; it preserves its original size and shape; it is readily available as autografts or homografts. Removal of bone grafts from the ilium is a relatively simple procedure; in addition, these grafts may be preserved by refrigeration and used as homotransplants. Recent reports have indicated the successful use of bone homografts preserved by refrigeration in a bone bank (Inclan,[6] 1942; Bush,[7] 1947; Wilson,[8] 1948; Converse and Campbell,[9] 1950). Homografts appear to give just as successful results as autografts. In both types the transplant serves as a mere framework, being entirely replaced by living bone from the host (Leriche and Policard [10]). Bone removed in excess at operation is cultured for organisms and stored in a sterile container in a bone bank at a temper-

4. DeVoe, A. G.: Personal communication to the authors.

5. White, J. C.: Late Complications Following Cranioplasty with Alloplastic Plates, Ann. Surg. **128**:743, 1949.

6. Inclan, A.: Use of Preserved Bone Graft in Orthopedic Surgery, J. Bone & Joint Surg. **24**:81, 1942.

7. Bush, L. E.: Use of Homogeneous Grafts: Preliminary Report on Bone Bank, J. Bone & Joint Surg. **29**:620, 1947.

8. Wilson, P. D.: Experiences with a Bone Bank, Ann. Surg. **120**:932, 1948.

9. Converse, J. M., and Campbell, R. M.: Experiences with a Bone Bank in Plastic Surgery, Plast. and Reconstruct. Surg. **5**:258, 1950.

10. Leriche, R., and Policard, A.: The Problem of the Normal Physiology and Pathology of Bones, Paris, Masson & Cie, 1926.

ature of −5 F. (−20 C.). Before transplantation the refrigerated bone should be removed from the freezing unit and defrosted at room temperature for one hour.

We have employed bone grafts in the form of a block of iliac bone taken from the inner table, comprising cortical and cancellous bone, and also as chips of cancellous bone (Mowlem[11]). Grafts are preferably removed from the inner aspect of the iliac bone. In our series of 14 cases, 16 bone-grafting operations were performed. Twelve of the grafts used were autografts and 4 were homografts. All gave equally successful results. In 1 case (case 8) part of the bone was removed when the previously irradiated soft tissues failed to heal and the graft became exposed. In another (case 4) a bone graft was placed over a defect communicating with the maxillary sinus; uneventful consolidation of the graft occurred. Bone grafts appear to maintain their original size and shape. In case 1, observed over a period of nearly three years, evidence of consolidation of the graft to the surrounding bone was seen (fig. 5).

Technic of Bone Grafting for Reconstruction of the Floor of the Orbit.—A cutaneous incision is made immediately below the eyelashes. The fibers of the orbicularis oculi muscle are split, and the anterior portion of the depressed orbital floor is exposed. The periosteum is incised, and the orbital contents are raised, with the periosteum, from the orbital floor. The eyeball is then elevated to the desired position, and a bone graft of suitable size is placed over the depressed floor. In raising the ptosed eyeball, the operator is guided by comparing its position with the unaffected eyeball and also by the degree to which the superior palpebral fold has been corrected. A block of cortical and cancellous bone is used, and any crevices or dead spaces left on the side of or beneath the graft are filled with small chips of cancellous bone.

Defects in the floor of the orbit are bridged by means of a bone graft. The peripheral limits of the orbital contents are exposed and freed from the underlying scar tissue in order that the eyeball may be raised to the desired position. The edges of the bony defect are exposed by elevating the periosteum; the bone graft is then wedged between the edges of the defect. Accessory grafts of cancellous bone chips may also be used to complete the reconstruction. Defects of the floor of the orbit thus repaired have varied in size; in 2 of our cases (cases 1 and 8) the entire orbital floor was reconstructed.

In cases of recession of the septum orbitale it is necessary to raise a flap of the periorbita; this flap, which is actually a blended periorbita and posterior extension of the septum orbitale, is turned forward

11. Mowlem, R.: Cancellous Chip Bone-Grafts: Report on 75 Cases, Lancet **2**:746, 1944.

and is placed in front of the inserted bone graft (fig. 4). In this manner the downward and backward pull of the lower lid is released.

A pressure dressing is applied for a period of at least five days after suture of the orbicularis oculi fibers and of the skin and temporary interpalpebral fixation.

The approach through an external incision in the lower lid gives the best exposure of the floor of the orbit. In 4 cases (cases 3, 5, 6 and 7) the defect in the infraorbital margin or the orbital floor resulted from a larger contour defect involving the maxilla and zygomatic bone. Bone grafts were successfully introduced through an intraoral incision made in the upper buccal sulcus (Converse [12]).

Figures 2, 6, 7 and 8 illustrate cases in which partial or total reconstruction of the floor of the orbit has been achieved.

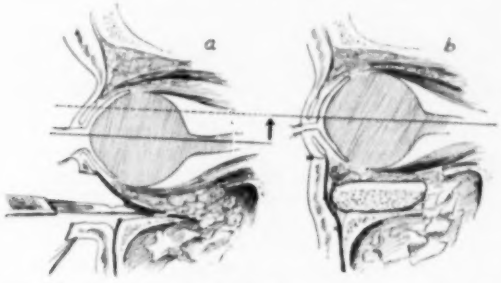

Fig. 4.—(*a*) freeing of the septum orbitale by elevation of a flap of periorbita; (*b*) use of a flap placed in front of the bone graft to raise the orbital contents. The retracted lower lid is thus freed.

REPORT OF CASES

Case 1.—*History.*—R. B., a white woman aged 37, consulted Dr. O. V. M. Schmidt with three complaints: obstruction of the left nasal fossa, a "squirming feeling" in her left cheek and pigmented spots on the skin of her face. The intranasal examination revealed a small mass protruding in the left middle meatus. The biopsy report, made on Oct. 16, 1945, was undifferentiated epithelial neoplasm.

She was admitted on Nov. 13, 1945 to the Memorial Hospital, where examination showed slight swelling of the left cheek; the left side of the palate was edematous. It was noted that the patient had slight bilateral exophthalmos. Roentgenographic examination showed erosion by a mass through the lateral and medial walls of the maxillary sinus.

Operation (November 19; Dr. Alfred Hocker): Bilateral ligation of the external carotid artery was done, and a lymph node was removed for microscopic examination.

12. Converse, J. M.: Restoration of Facial Contour by Bone Grafts Introduced Through the Oral Cavity, Plast. & Reconstruct. Surg., to be published.

Operation (December 3; Dr. Alfred Hocker): A tumor in the left maxillary sinus invaded the floor of the left orbit and perforated the roof of the left side of the mouth.

A Webber-Ferguson incision was made, and the flap of the left cheek was reflected. With cautery the hard palate was incised. With a Gigli saw the roof of the mouth was cut on the left side. The flap was retracted posteriorly, and the left zygomatic bone was cut with a Gigli saw. With the chisel the frontal process of the superior maxilla was cut. The specimen was excised and examined. It was decided to preserve the left eye. To support the globe, a flap of muscle and fascia was developed from the left temporal muscle and sutured with wire to the inner angle of the orbit. The defect was closed by resuturing the flap. The skin was closed with interrupted fine dermalon* and the cavity packed for hemostatic purposes. The postoperative course was relatively uneventful. There was some edema about the lids of the left eye.

Postoperative Course: An ophthalmologist saw the patient on December 20. She complained of diplopia, discharge and pain near the lateral canthus. The left eye moved in all directions. Single vision was obtained only in the left lower temporal field; the greatest diplopia was in the right upper field of gaze. The double vision was attributed to weakness of the left inferior oblique muscle. A moderate degree of lagophthalmos was present, but the cornea was protected.

Preoperative roentgenograms (Oct. 8, 1945) showed widespread destruction of bone about the left maxillary sinus. A portion of the floor of the maxillary sinus, the inferior part of the lateral wall, a wide portion of the medial wall and a small portion of the anterior wall of this sinus had been destroyed. There was thinning of the infraorbital ridge, and involvement of the orbital floor was suspected. Extension of the disease into the pterygoid region was suspected. There was accompanying infiltration of the posterior ethmoidal cells on the left, and a portion of the anterior ethmoidal group was involved.

A surgical specimen from the region of the left maxillary sinus was diagnosed as a mucoepidermoid carcinoma. Decalcified sections showed invasion of the floor of the sinus.

After the operation a denture with an obturator was made by Dr. Andrew J. Ackerman.

Examination.—We first examined the patient on April 10, 1947 (fig. 2*A*). Examination revealed prominent flattening of the entire middle third of the face on the left side with a conspicuous depression beneath the left eye. On palpation the lower border of the lateral wall of the orbit and the anterior portion of the zygomatic arch could be felt beneath the skin. Palpation revealed the absence of the entire floor of the orbit, as well as the maxilla and zygomatic bone. The dental prosthesis restored the contour of the left side of the upper lip and of the lower portion of the cheek. On removal of the denture the depression of the left side of the face was increased, owing to the lack of support of the soft tissues. Intraoral examination showed the absence of a third of the palate on the left side and a clean, completely epithelized cavity, with no sign of recurrence.

Examination showed ptosis of the left eyeball. Beneath the left supraorbital ridge was a deep depression of the supratarsal skin with deepening of the superior palpebral fold. There was depression on the left side beneath the orbital contents and in the left zygomatic region. The left interpalpebral fissure was widened. The left eye, however, did not appear to be in a greater state of exophthalmos than the right. There was approximately 5 mm. of depression of the left eye

at the external canthus. At the time of examination the patient did not complain of diplopia, although she stated that diplopia was present when the eye became fatigued.

Examination in the eye muscle clinic revealed limited adduction of the left eye. Measurement in the cardinal fields of gaze showed paresis of the left internal rectus, left inferior oblique and left superior rectus muscles. She fused in casual gaze most of the time. Maintenance of fusion was easier for near vision and below the horizontal plane and on looking to the left.

The decision was made to reconstruct the floor of the orbit, the upper portion of the maxilla and the zygomatic prominence by means of grafts from the iliac bone. The dental prosthesis and obturator which the patient wore in order to fill the palatal defect restored the contour in the alveolar area and the lower portion of the cheek. Such a denture cannot sufficiently support the sagging of orbital contents, nor can it maintain the contour of the upper portion of the cheek.

Operation.—With the use of intratracheal anesthesia, with the tube passed through the right nasal airway, an incision was made along the scar left by the operation for resection of the maxilla. This scar extended along the margin of the lower eyelid to a point beneath the medial canthus and then curved downward along the base of the lateral wall of the nose to the base of the ala. After incision of the skin in the lower lid, the fibers of the orbicularis oculi muscle were split longitudinally. The skin flap, including the layer of the muscles of expression, was raised. The orbital contents were freed from adherent scars, and the dissection was extended into the posterior portion of the orbit. The freed orbital contents could then be raised, and it was noted that in so doing the superior palpebral fold became filled by the raised eyeball, assuming an aspect similar to the fold on the right side. By comparison with the unaffected (right) eye, the degree of raising necessary to insure adequate correction could be estimated. Laterally, the anterior portion of the zygomatic arch was exposed by raising the periosteum. The periosteum was also raised from the bone extending in front of the lacrimal crest and over the frontal process of the maxilla.

Through an incision over the right iliac crest, the periosteum along the crest was incised and raised over the inner table of the ilium. Bone grafts comprising the inner table of the ilium and cancellous bone were then resected. The periosteum was sutured, and the wound was closed layer by layer.

A piece of iliac bone, suitably shaped to restore the floor of the orbit, was wedged between the anterior tip of the zygomatic arch, laterally, and the frontal process of the maxilla, medially. No means of fixation other than the tight fit of the graft was employed. The depression left below the orbital floor was filled with cancellous bone chips approximately 1 cm. in diameter. Over these contour-restoring bone chips was placed, as an overlay, another shaped bone graft, comprising the inner table of the ilium, with its convex cancellous surface placed outward and its cortical surface inward. Careful suture of the muscle layer and of the edges of the skin flap to the edges of the surrounding skin was then done. A temporary suture of the eyelids insured protection of the cornea, and a pressure dressing was applied. The dental prothesis was maintained in position, and during the operation the upper portion of the obturator could be felt immediately beneath the soft tissues. It was maintained in position throughout the operation and during the postoperative period in order that it might aid in the support of the bone grafts. At the end of the operation a feeding tube was passed into the left nasal fossa and into the stomach in order to minimize mobilization of the grafts by mastication and deglutition. Pressure was maintained over the face for a period of seven days, and sutures were removed and pressure was reapplied for a second period of

seven days. At the end of fourteen days it was found that the bone grafts were fairly adherent, and no further dressing was done.

Operative Result.—On examination, at the end of seven days after operation, diplopia was present intermittently. By the end of the second postoperative week all diplopia had subsided and a wide range of third grade fusion was demonstrable. Likewise, the enophthalmos was corrected. A small residual widening of the vertical width of the left interpalpebral fissure was treated six weeks after the bone grafting by a tongue and groove type of lateral tarsorrhaphy. Three months after the bone grafting, a small dermal graft was inserted over the left zygomatic prominence further to improve contour.

Restoration of contour has been satisfactory (fig. 2*B*), and the patient has been able to resume binocular vision and perform her work in a satisfactory manner.

Fig. 5 (case 1).—Roentgenogram showing consolidation of bone grafts used to reconstruct the floor of the left orbit, taken two years and six months after transplantation.

Roentgenographic examination two years and six months after operation showed that the bone grafts have become integrated with the surrounding bones (fig. 5).

Case 2.—J. M., a white girl aged 18, was referred to the plastic surgery clinic in October 1947 for the treatment of congenital enophthalmos (right side), deformity of the right orbit and contracted socket. Previous operations by various surgeons had failed to rectify the deformity or create a useful socket. The left eye was conspicuous, owing to a congenital coloboma of the iris and lens. The fundus showed some medullation of nerve fibers about the disk. Vision was normal. The mother of the patient had congenital anomalies of the distal joints of her extremities.

The temporal rim of the right orbit was recessed approximately 1 cm. Remnants of both lids were held in the apex of the orbit by dense adhesions, and the eyelashes were gathered in a circular mass at the apex of the orbit.

The roentgenologic picture was in keeping with the physical findings. The right orbit was smaller in volume than the left.

On Dec. 4, 1947 a bone autograft was transferred from the right ilium to the right orbit. The graft was cut into chips of such size as to rebuild the contour of the orbital margin and replace the deficient soft tissues deep in the orbit.

Three months later, in March 1948, a blepharoplasty was done by transplanting the tarsus from the left upper lid to the right lower lid as a free graft. Healing was uneventful. At a third procedure, in June 1948, transplantation of lashes was done. The last procedure, in December 1948, one year after the bone grafting, consisted in transplantation of mucous membrane from the mouth to line the socket. After two months of fitting acrylic implants of graduated increased size, the socket was of sufficient size to accommodate a prosthesis. The technic of esthetic correction of unilateral anophthalmos by ophthalmoprosthesis (Murphey and associates,[13] 1948) was utilized as the terminal phase of the treatment.

Case 3.—M. G., aged 30, was struck in the right cheek by repeated fist blows in December 1947. She had pain, swelling and ecchymosis of the eyelids and subconjunctival hemorrhage, but she did not think seriously of the injury and she received no treatment. About ten days later, after the swelling had subsided, she noticed flattening of the right cheek with some difficulty in opening her mouth, ptosis of the right lower eyelid and slight deviation to the left of the philtrum of her upper lip and slight drooping of the right corner of her mouth. She consulted the dental clinic at Bellevue Hospital in April 1948 and was referred to the plastic surgery unit. Clinical examination revealed a bony depression extending over the zygomatic area. Palpation revealed that the zygomatic bone, as a result of a fracture dislocation, was depressed backward and downward. The fragments were solidly united. Along the infraorbital margin, a notching was noted at the point of junction of the zygomatic bone with the maxilla. There was a depression of the lateral portion of the orbital floor of approximately 1 cm.

It was decided to restore the contour by means of bone grafts rather than attempt to loosen the zygomatic bone and replace it. On May 26, with the patient under endotracheal anesthesia, bone autografts were removed from the inner aspect of the right iliac bone. An incision was made in the labial aspect of the right upper vestibule approximately 8 cm. in length, extending laterally from the frenulum. The mucosa was dissected from the orbicularis oris muscle until the periosteum of the maxilla was exposed. An incision was made through the periosteum, which was then elevated over the whole anterior surface of the maxilla and zygoma. The infraorbital neurovascular bundle was exposed and resected. With good illumination, the depressed infraorbital margin could be visualized. One bone graft of cancellous and compact bone was shaped and fitted to restore the depressed infraorbital margin. Another bone graft was shaped to restore contour over the zygoma and maxilla. Numerous chips of cancellous bone were placed between these two main fragments. An interpalpebral suture was placed closing the eyelids and a pressure dressing applied over the face. Pressure dressing was maintained for a period of eight days, after which dressings were dispensed with.

The patient made an uneventful recovery, and the restoration of contour has been very satisfactory. The patient was seen one year after the operation, and the restored contour was found to have been maintained very well.

Case 4.—D. B., a white boy aged 12 years, was admitted on June 20, 1948, after having been struck over the right side of the face with a baseball bat on June 18, 1948. He was first seen in the plastic surgery clinic on June 23. Examination

13. Murphey, J. M.; Newton, F. H.; Steel, C., and Hawk, P. P.: Esthetic Correction of Unilateral Enophthalmos by Ophthalmoprosthesis, Arch. Ophth. **40**:497 (Nov.) 1948.

showed pronounced swelling and ecchymosis of the right cheek and eyelids, chemosis of the conjunctiva with prolapse through the closed lids and subconjunctival hemorrhage. Palpation through the edematous tissues revealed depression of the right zygoma and of the entire right infraorbital margin. A previously sutured laceration of the right lower eyelid showed signs of inflammatory reaction. Roentgenologic examination revealed a severely comminuted, depressed fracture of the right zygoma and infraorbital margin.

On June 24, with the patient under intratracheal anesthesia, the right maxillary sinus was entered through a Caldwell-Luc approach. The comminuted fragments of the zygoma and of the orbital floor were seen protruding through the mucosa of the maxillary sinus. A nasoantral window was then made in the right inferior meatus. Through an incision in the mucosa overlying the tuberosity of the maxilla,

Fig. 6.—*A*, loss of the infraorbital margin and of a portion of the floor following osteomyelitis; *B*, restoration of contour by reconstruction with bone grafts.

an elevator was placed beneath the right zygoma, elevating the displaced bony fragments. The comminuted fragments of the floor of the orbit were raised, and the maxillary sinus was packed with petrolatum gauze strip, one end being brought out through the nasoantral window. The prolapsed, chemotic conjunctiva was replaced, and the lids were sutured together with interrupted silk sutures. The sutures were removed from the previously sutured, lacerated right lower lid. The packing in the antrum was removed seven days later.

Despite antibiotic therapy, suppuration followed this operation, and an appreciable amount of bone was eliminated through sequestration. Consolidation of the comminuted fragments did not occur, and the orbital floor descended. After the edema subsided, an infraorbital depression became evident, with retraction of the lower lid, but with no ectropion, diplopia or disturbances of the extraocular muscles (fig. 6*A*).

On Nov. 18, 1948 bone grafts removed from the right ilium were used to reconstruct the infraorbital defect. After the scar tissue beneath the orbital contents was excised, an opening into the maxillary sinus was noted. One bone graft, placed in contact with surrounding bone stripped of its periosteum, was used to bridge the defect, and restoration of contour was completed with small chips of cancellous bone.

After this successful operation a downward retraction of the right medial canthus, due to scar forming between the lid and the bone graft, was corrected by a full thickness skin graft taken from the left upper lid. The final result was satisfactory (fig. 6*B*), although recently a slight tendency toward vertical shortening of the right lower lid has been noted.

Case 5.—C. C., a white woman aged 22, referred by Dr. Gaston Duchet, of Paris, France, had a history of "osteomyelitis" of the right maxilla at the age of 2 years. The right side of her face was less well developed than the left. The right zygomatic area was flattened, and the right infraorbital margin was undeveloped, appearing to be depressed backward.

On Oct. 20, 1948 operation was done at the American Hospital in Paris, France. With the patient under endotracheal anesthesia, bone grafts were removed from the inner table of the right ilium. An incision through the mucosa was made in the right oral vestibule. The periosteum was exposed, incised and elevated over the entire surface of the maxilla and zygomatic bone on the right side. The infraorbital nerve was preserved. The entire infraorbital margin was exposed. One bone graft was shaped and placed over the infraorbital margin. A second, larger bone graft was carved to restore the contour of the zygomatic and maxillary areas. It was placed with the cortical surface against the maxilla and the cancellous surface facing outward. Numerous chips of cancellous bone were packed between these two main grafts, fitting into all interstices and crevices. The vestibular incision was sutured and pressure dressing applied over the entire right side of the face.

The day after the operation the patient's temperature rose to 104 F. Examination revealed acute pharyngitis. Antibiotic treatment was instituted with penicillin and streptomycin, and in forty-eight hours the temperature returned to normal. It is interesting to note that, despite an acute inflammatory episode and the fact that the bone grafts were placed through an incision made in the oral cavity, the bone grafts proceeded to consolidate uneventfully. The improvement in contour in this case was very satisfactory.

Case 6.—M. G., a white girl aged 17, was referred by a physician in Paris, France, for the repair of a facial deformity consisting of noticeable underdevelopment of the right maxillary and zygomatic bones with resulting marked facial asymmetry. At the age of 5 years the patient had lost bone through sequestration following osteomyelitis. Examination showed a small maxilla and zygoma on the right side and recession of the right infraorbital margin with a depression in the right infraorbital region. A scar extended over the right zygomatic bone (fig. 7*A*).

Complete ophthalmologic examination on Nov. 4, 1948 revealed no disturbance of vision or muscular balance. The interpalpebral fissures were of equal width except in the outer one third, where the right lower lid was retracted over the area of bone deficiency.

On November 15 the scar over the right zygoma was excised and the anterior surface of the maxilla and zygoma was exposed by raising the periosteum, care being taken to avoid injury to the infraorbital nerve and vessels. Most of the lower rim of the orbit and part of the floor were found to be absent. The orbital contents were raised by elevating the periosteum from the floor. A bone autograft removed from the ilium was placed over the floor of the orbit and shaped to restore the

orbital margin. A second, larger graft was placed over the maxilla and zygoma. Numerous chips of cancellous bone were used to fill the intervening crevices and further to restore contour. A pressure dressing was applied after closure of the wound in the skin and interpalpebral suture. Consolidation of the grafts and the esthetic result were satisfactory. On April 11, 1949 bone homografts in the form of chip bone grafts from the bone bank were placed through an incision in the upper part of the oral vestibule on the right side to fill a depression of the lower part of the maxilla above the alveolar process. Restoration of contour in this case has been very satisfactory (fig. 7*B*).

Case 7.—C. T., a white girl aged 16, was treated in collaboration with Dr. Joseph D. Kelly. The patient showed a deformity of the left orbital floor and

Fig. 7.—*A*, deformity of the right side of the face due to underdevelopment of the maxilla and zygomatic bone as a result of osteomyelitis in childhood. Note loss of bone in the infraorbital margin and enophthalmos.

B, restoration of contour obtained by transplantation of three bone autografts and homografts. Note correction of enophthalmos of the right eye.

infraorbital area due to loss of bone affecting the middle third of the orbital floor, the result of "osteomyelitis" at the age of 5 months. Infection of the bone and sequestration were thought to have resulted from infection of the maxillary sinus at that age. Drainage of a collection of purulent discharge was done through an intraoral vestibular incision on that side. Recurrent purulent drainage occurred every two months during the subsequent years.

Repair of the bony defect was undertaken primarily for cosmetic purposes. On Sept. 11, 1947 a bone graft removed from the right ilium was placed in the defect through an incision made in the left oral vestibule after the periosteum had

been raised from the anterior wall of the maxilla. The defect along the infraorbital margin and floor of the orbit was well visualized, and one main bone graft surrounded by multiple small cancellous chips was placed in the defect.

A satisfactory improvement in the contour resulted from this operation, and further improvement was obtained by the placing of a small graft of fascia lata, on Oct. 28, 1948.

Case 8.—M. T., a white nurse aged 40, was referred to Dr. Rufus Morrow in June 1946, after a nasal hemorrhage. A diagnosis of undifferentiated squamous cell carcinoma of the left maxillary sinus was made as a result of biopsy. The patient refused to undergo surgical treatment and was given radiation. In November 1946 the patient began to show signs of radiation necrosis of the left maxilla.

On July 29, 1948 a sequestrectomy was done, a large portion of the necrosed left maxilla being removed. Subsequently, the entire floor of the left orbit sequestrated spontaneously. During the following weeks the contents of the left orbit became depressed, and the left eyeball was subjected to a downward rotation. Ophthalmologic examination revealed no abnormality of the right eye. The height of the left interpalpebral fissure was increased by retraction and cicatrization of the base of the lower lid. There was deepening of the supratarsal sulcus, secondary to ptosis of the globe. The mobility of the left eye was limited by scarring in the inferior rectus muscle. The action of the left inferior oblique was also greatly diminished. Left hypotropia of approximately 50 D. was present with the eye in the primary position. A defect in the cheek formed an abnormal termination of the proximal extremity of the left lower lid. Internal examination showed no abnormalities. Up to the middle of November 1948, a moderate degree of lagophthalmos produced no symptoms. Although no diminution in corneal sensation was elicited, an area of ulceration appeared superior to the limbus at 6 o'clock. The eye became red and painful and did not respond to local treatment. As a therapeutic measure and as a preventive of further corneal damage, interpalpebral adhesions across the left interpalpebral fissure were surgically created on December 3. The adhesions rapidly epithelized, and no further corneal damage has made its appearance since that time. The adhesions are to be preserved until closure of the defect in the cheek and reconstruction of the orbital floor have been completed.

On Jan. 13, 1949, with the use of local anesthesia an incision along the upper margin of the defect was made. The remainder of the frontal process of the maxilla and the anterior end of the zygomatic arch were exposed. The orbital contents were freed from scar tissue and raised by a refrigerated bone homograft wedged between the zygomatic arch and the frontal process of the maxilla. After careful suture of the wound, a pressure dressing was applied. The poorly vascularized covering of soft tissues failed to heal over a portion of the wound, and the exposed bone was extruded. A sufficient amount of bone survived to give support to the orbital contents.

Case 9.—V. L., a white man aged 41 was referred in June 1948, through the courtesy of Dr. Derrick Vail, for treatment of diplopia, dacryocystitis and bony deformity of the left orbital margin and floor. The injury had resulted from the explosion of a building two years previously. The original injury was of a serious nature and was complicated by fracture of the skull. Between the time of the injury and the patient's first visit twenty-three operations had been performed. Among them were slitting of the lower canaliculus of the left eye and the implantation of bovine cartilage to the left cheek.

On first examination, vision was corrected by lenses to 20/20 in each eye. Prisms incorporated in the lenses helped the patient avoid diplopia. The left lower

lid was retracted by the scar and the underlying fracture. The left globe was lower than the right, and there was limitation of motion in the field of action of the left inferior oblique muscle.

The dacryocystitis on the left was eliminated by dacryocystorhinostomy on June 28. At the time of the grafting of bone to the floor of the left orbit, on Jan. 12, 1949, all evidence of infection of the lacrimal tract had been replaced by normal lacrimal drainage. The section of bovine cartilage "floating" beneath the skin of the left cheek was removed at the operation. Bone from the left ilium was used to rebuild the floor of the orbit. There was so much shortening of the lower lid that lengthening of the septum orbitale required covering by a free full thickness skin graft from the opposite upper lid.

On the last visit, in October 1949, the patient was asymptomatic and the graft was smooth and solid. The procedure failed to restore the deepening of the left supratarsal sulcus. It is planned, in a subsequent procedure, to transplant a fascial or dermal graft to complete the eradication of the deformity.

Case 10.—S. J., a Philippine scout aged 25, had had a deformity of the left cheek and diplopia since an injury sustained in an automobile accident in June 1948. Examination revealed the typical deformity and left hypotropia. There was some limitation of rotation in the field of action of the left inferior rectus muscle. Vision was normal in each eye, and there was no evidence of infection of the lacrimal tract. With the patient under general anesthesia at Fort McKinley Hospital, Manila, on March 15, 1949, a bone autograft from the left ilium was implanted. Healing was uneventful, and recovery was complete.

Case 11.—L. P., a 26 year old infantry officer in the Greek army, referred through Dr. R. Townley Paton, was wounded by Communist rifle fire on Aug. 11, 1948. On his arrival in New York in September 1949, the patient presented absence of the right eyeball and the floor and rim of the right orbit inferiorly and laterally. The eyelids had been replaced by advancement of neighboring skin flaps. The lashes were missing. The zygomatic prominence was replaced by a deep subcutaneous depression, due to the absence of bone. The zygomatic arch was fractured and telescoped, creating impingement on the temporalis muscle. The right brow was normal but poorly supported in its temporal half, owing to absence of bone. The right conjunctival sac was demonstrated through a small fistula at the site of the right internal canthus. By sounding, it was shown to be about one third its normal size.

On Sept. 16, 1949 a bone autograft from the right ilium was used to restore the contour of the right malar prominence and the floor of the right orbit. The remainder of the graft was placed in the bone bank for storage. The amount of bone which could be implanted was somewhat limited by the presence of tension on the overlying skin. Healing was uneventful.

Transplantation of cilia from each brow to the future lid margins was done on November 20. Healing took place without the usual temporary loss of the cilia.

By December 13 sufficient stretching of the skin and subcutaneous tissues had taken place so that bone grafting could be completed. At this procedure the prominence of the zygomatic arch was reduced with an osteotome. The right supraorbital ridge was restored, and additional bone chips were grafted to the malar prominence. Between the two osteoplastic operations, a period of nearly three months, the bone had been stored in the bone bank. Healing was uneventful.

The final stage of enlargement of the socket and opening of the interpalpebral fissure remains.

Case 12.—L. P., an officer from the Chilean army, aged 26, was referred through Dr. Ramon Castroviejo and Dr. Douglas Parker. The patient gave a history of

injury in an automobile accident on Nov. 16, 1948, when he received an injury to the right infraorbital region.

In Santiago an operation was performed ten days after the injury. A second operation was done in Chile in January 1949 for the purpose of restoring the contour of the right cheek with a bone graft from the right ilium.

When we first examined him, on Oct. 7, 1949, the patient complained of diplopia and deformity of the right orbit. Vision was 20/60 in the right eye and 20/20 in the left eye. In addition to 12 mm. of enophthalmos of the right eye, there were prominent ptosis of the globe, paresis of the right inferior rectus and narrowing of the right interpalpebral fissure of 4 mm. when the eyes were in the primary position. The right nerve head was pale. The cornea was less sensitive than that of the left eye. The frontalis muscle of the right side also showed striking underaction with wrinkling of the forehead. The lacrimal ducts were normal.

Roentgenologic examination revealed the presence of a depressed, comminuted fracture of the floor of the right orbit with the orbit and orbital margin on this side lower than on the left.

After transplantation of a bone autograft from the left ilium to the floor of the right orbit, with the patient under thiopental sodium (pentothal®) anesthesia, on Nov. 7, 1949, healing was uneventful. The ptosis of the right globe was corrected,

Fig. 8.—*A*, appearance of the patient after three unsuccessful attempts to correct a deformity due to loss of the anterior portion of the floor of the right orbit and shortening of the septum orbitale caused by a bombing injury.

B, improvement obtained by restoration with bone grafts and release of the septum orbitale, as shown in figure 4. Further improvement can be obtained by a lateral tarsorrhaphy to narrow the palpebral fissure.

and the interpalpebral fissure in the primary position measured the same as that on the opposite side. The right supratarsal sulcus remained deeper than normal, and the right eye presented hypertropia of 30 D. On Jan. 17, 1950 recession of the right superior rectus muscle and resection of the right inferior rectus muscle corrected the hypertropia cosmetically. The remaining deformity consists of about 7 mm. of enophthalmos on the right side.

Case 13.—J. B., a French physician aged 28, was wounded during the Battle of France, in 1940, by a bomb explosion, suffering injuries to the right orbit. Sequestration of bone followed infection and suppuration. In 1947, in France, a skin graft was placed in the right lower lid, in an attempt to correct the downward pull on the lid.

When he was first examined in the plastic surgery clinic, on Sept. 5, 1949, it was noted that the rim and the anterior portion of the floor of the right orbit were missing, the right lower lid was pulled downward and backward and the right palpebral fissure was enlarged. The skin of the right lower lid was loose, and the downward contraction of the lid was interpreted as being due to recession and shortening of the septum orbitale (fig. 8*A*).

The patient complained of ocular fatigue after reading and of occasional diplopia. There was a high degree of mixed astigmatism. Fusion was unstable, in accordance with relatively fixed amblyopia of the right eye. Exotropia of small magnitude, probably present before the injury, existed as a little apparent deformity. In view of the patient's age, the presence of amblyopia and the unstable fusion, suppression of the right eye was advocated as a means of treatment.

On September 26, with the use of local anesthesia, through an incision below the right lower lid, the margin of the orbital floor was exposed and the periosteum raised. The orbital contents were freed from scar tissue in the area where the orbital floor had been destroyed. The septum orbitale was lengthened by raising a flap of periorbita, as illustrated in figure 4. The anterior portion of the floor and the rim of the orbit were reconstructed with bone homografts preserved for three months in the bone bank. After suture of the lid incision and interpalpebral suture, a pressure dressing was applied. The bone grafts had become consolidated with the adjacent area at the end of two weeks. Correction of the deformity was successful in this case (*fig. 8 B*).

CASE 14.—J. F., a Puerto Rican aged 25, referred through Dr. Ramon Castroviejo and Dr. Douglas Parker, had sustained a fracture of the floor of the right orbit in an aircraft crash in June 1949.

After the injury diplopia was present, but gradually subsided. When the patient was first examined, on Nov. 26, 1949, vision was normal in each eye. The deformity of the right orbit consisted of ptosis of the globe, enophthalmos of 7 mm. and a deep recess in the area of the supratarsal sulcus. The muscular balance was not disturbed except for a convergence insufficiency due to slight weakening in the action of the right medial rectus muscle. A horizontal scar at the collar line showed some elevation, due to keloid proliferation.

Roentgenographic examination demonstrated a depressed, comminuted fracture of the floor of the right orbit. The margin of the orbit was little disturbed.

On November 30, a homograft from the bone bank was used to replace the floor of the right orbit. Healing was uneventful. Horizontal diplopia, present at the first dressing, had completely disappeared within a week.

Observation on December 14 showed that the position of the globe was excellent, the enophthalmos was corrected and the supratarsal sulcus had a normal contour. The right lower lid had begun to show evidence of ectropion. The cause of this ectropion is not clearly understood. Since there was no disturbance of the orbital margin in the original roentgenographic examination and a second roentgenogram, on December 20, showed the graft in excellent position, one is not obliged to attribute it to a bony malposition. In view of the presence of the keloid in the scar of the neck, perhaps a tendency to excess formation of scar tissue may be an explanation. The cutaneous scar, however, appeared normal.

On December 20 it was decided that surgical correction of the ectropion of the right lower lid should be done. An incision parallel, and 3 mm. inferior, to the lid margin was extended from the region of the internal to the external canthus. The lid margin was firmly held to the periosteum of the orbital margin by a dense matting of fibers of the distorted orbicularis muscle. When it was dissected free, the septum orbitale appeared to be nearly normal. Interpalpebral adhesions were created, and a full thickness graft of skin from the opposing upper lid was placed in the defect over the raw surface of the septum orbitale. Since the patient had a tendency to keloid formation, it was considered unwise further to disturb the orbicularis or to excise additional subcutaneous scar which existed between the orbital margin and the overlying skin.

On December 25 the sutures were removed. The graft appeared healthy; the adhesions were healing, and the position of the right lower lid was excellent. Before the interpalpebral adhesions are severed, two months will be allowed for healing and local massage.

SUMMARY

Conditions producing distortion or loss of the floor of the orbit are reviewed. Deformity, orbital disturbances and diplopia result from disorganization or loss of the orbital floor. Clinical and roentgenographic methods of evaluation of the deformity are discussed. The technic of reconstruction of the floor of the orbit by autografts and homografts of bone is described in 14 cases in which it was successful.

PENETRATION OF CHLORAMPHENICOL U. S. P. (CHLOROMYCETIN*) INTO THE EYE

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THE NUMBER of antibiotic agents is constantly increasing. At present there are available, at least for clinical investigation, the following antibiotics: penicillin; streptomycin; dihydrostreptomycin; neomycin; polymyxin B, or aerosporin; tyrothricin; bacitracin; aureomycin, and chloramphenicol U. S. P. (D-[—]-threo-2-dichloroacetamido-1-para-nitrophenyl-1,3-propanediol), also known as chloromycetin.* Many other new antibiotics are still not ready for clinical investigation but are under study at the present time. It appears that more antibiotics will rapidly become available in the future. Many factors keep the problem of antibiotic therapy from being a simple one. A few years ago it was easy to decide which antibiotic to use in a particular case on the basis of whether the infecting organism was gram-positive or gram-negative. Now, however, one must choose between several antibiotics for gram-positive organisms, several for gram-negative organisms and still others for viruses and rickettsias. One must now decide which antibiotic will be the most effective, the least toxic, the easiest to administer and the cheapest. There still remains the problem of whether or not a combination of various antibiotics would not be better than a single one in the treatment of a particular infection.

In an effort to simplify the problem, Long and his associates,[1] on the basis of available data, have prepared a number of tables which show the first, second and third choices among the antibiotics for various types of infections. In these tables, however, there are many blank spaces, which are due to the fact that much of the data is still unavailable. The dosage schedules recommended at present are based

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Presented at the Wills Eye Conference, March 17, 1950.

Chloromycetin* was supplied by Parke, Davis & Company, Detroit.

From the Research Laboratories of the Wills Hospital and Harrison Department of Surgical Research, University of Pennsylvania School of Medicine.

1. Long, P. H.; Chandler, C. A.; Bliss, E. A.; Bryer, M. S., and Schoenbach, E. B.: The Use of Antibiotics, J. A. M. A. **141**:315 (Oct. 1) 1949.

on experimental data showing that these schedules will produce satisfactory blood concentrations and on clinical data revealing that these schedules result in clinical cures in many cases. The ophthalmologist has additional problems because of the peculiarities of the blood-aqueous barrier, for the presence of adequate blood concentrations does not guarantee adequate concentrations in all the ocular fluids and tissues that may be involved in the infectious process. In other words, as ophthalmologists we are concerned not only with whether or not the organism responsible for the infection in the ocular tissues is susceptible to the drug that we have chosen but with whether the drug which we know to be effective against the organism elsewhere in the body will penetrate into the involved ocular tissues in sufficient concentration to bring about the desired result. It is not enough for the ophthalmologist to realize the toxic reactions from systemic administration of antibiotics, e. g., on the kidneys, blood and skin; he must also keep in mind the possibilities of local toxic reactions in the ocular tissues when this drug is administered systemically or locally. The intraocular penetration and tolerance have been studied for penicillin,[2] streptomycin,[3] bacitracin,[4] and aureomycin.[5] The present study is concerned with the intraocular penetration of chloromycetin[6] when locally or systemically administered and with a consideration of possible toxic reactions following its local and systemic use.

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2. (*a*) Leopold, I. H.: Intravitreal Penetration of Penicillin, and Penicillin Therapy of Infections of Vitreous, Arch. Ophth. **33**:211 (March) 1945. (*b*) Leopold, I. H., and LaMotte, W. O., Jr.: Penetration of Penicillin in Rabbit Eyes with Normal, Inflamed and Abraded Corneas, ibid. **33**:43 (Jan.) 1945. (*c*) Sorsby, A.: Penicillin, in Modern Trends of Ophthalmology, New York, Paul B. Hoeber, Inc., 1948, vol. 2. (*d*) Struble, G. C., and Bellows, J. G.: Studies on the Distribution of Penicillin in the Eye, J. A. M. A. **125**:685 (July 8) 1944. (*e*) von Sallmann, L.: Controversial Points in Ocular Penicillin Therapy, Tr. Am. Ophth. Soc. **45**:570, 1947. (*f*) von Sallmann, L., and Meyer, K.: Penetration of Penicillin into the Eye: Further Studies, Arch. Ophth. **34**:195 (Sept.) 1945; (*g*) Penetration of Penicillin into the Eye, ibid. **31**:1 (Jan.) 1944.

3. (*a*) Bellows, J. G., and Farmer, C. J.: Streptomycin in Ophthalmology, Am. J. Ophth. **30**:1215, 1947. (*b*) Leopold, I. H., and Nichols, A.: Intraocular Penetration of Streptomycin Following Systemic and Local Administration, Arch. Ophth. **35**:33 (Jan.) 1946.

4. Bellows, J. G., and Farmer, C. J.: Use of Bacitracin in Ocular Infections, Am. J. Ophth. **31**:1070, 1948. Locke, J. C.: Experimental Studies with Antibiotics: Bacitracin, Streptomycin, Penicillin, and Antibiotic Mixtures in Intraocular Infections with Penicillin-Resistant Staphylococci, Am. J. Ophth. **32**:135 (June, pt. 2) 1949.

5. (*a*) Bellows, J. G.; Richardson, V. M., and Farmer, C. J.: Aureomycin in Ophthalmology, Am. J. Ophth. **33**:273, 1950. (*b*) Braley, A. E., and Sanders, M.: Aureomycin in Ocular Infections, J. A. M. A. **138**:426 (Oct. 9) 1948. (*c*) deRoetth, A., Jr.: Penetration of Aureomycin into the Eye, Arch. Ophth. **42**:365 (Oct.) 1949.

METHOD OF INVESTIGATION

Local Application.—Solutions: Drops of chloramphenicol dissolved in propylene glycol in a concentration of 50 mg. per cubic centimeter and of chloramphenicol in aqueous solution in a concentration of 2.5 mg. per cubic centimeter were instilled into rabbit eyes every five minutes for six doses. At a designated time the eyes were flushed with isotonic sodium chloride solution U. S. P., 2 drops of 0.5 per cent tetracaine hydrochloride solution were instilled into each eye, and approximately 0.2 cc. of aqueous humor was withdrawn at stated intervals with a 27 gage needle and a tuberculin syringe. For subconjunctival injections, solutions of the same concentration in propylene glycol and in water were used. Two-tenths cubic centimeter was injected under the conjunctiva in the region of the superior rectus muscle, and at designated intervals the eyes were flushed with isotonic sodium chloride solution and aqueous humor was withdrawn. Tetracaine hydrochloride was used for local anesthesia.

Iontophoresis: The cathode pole was applied to the eye electrode. The solution used contained chloramphenicol in a concentration of 2.5 mg. per cubic centimeter of water. A current of 3 milliamperes was maintained for five minutes with each solution.

Abrasion Studies: In order to determine the importance of the epithelial barrier, solutions and ointments were applied to rabbit eyes with normal and with abraded corneas. A standard abrasion was used, as described in previous papers.[6] The ointments contained 50 mg. of chloramphenicol per gram. The ointment vehicles were petrolatum and a 75:25 mixture of hydrous wool fat U. S. P. and propylene glycol.

Systemic Administration.—Systemic administration was made by the intravenous route, using solutions of chloromycetin[8] in propylene glycol. Doses of approximately 50, 100 and 150 mg. per kilogram of body weight were injected into rabbits. Also, 0.5 Gm. was given by the oral route to rabbits weighing approximately 4 Kg. Specimens were withdrawn from the vitreous and aqueous at designated times, and the individual ocular tissues were analyzed, as previously described. A cup method of assay was used, as described by Randal and co-workers[7] for ocular fluids and tissues. Blood assays were made by the serial dilution method.[6]

RESULTS

Intravenous Administration.—It is evident from a study of table 1 that chloramphenicol when injected intravenously into rabbits in concentrations of 50 mg. per kilogram of body weight penetrates rapidly into the anterior chamber. It is detectable in a fairly high concentration in the aqueous humor within thirty minutes. This concentration rapidly falls, so that by the end of four to six hours little of the active drug is still present in the aqueous humor.

6. Leopold and LaMotte.[5b] Leopold and Nichols.[5b]

7. Randal, W. A.; Nielson, J. K.; Kirschbaum, A., and Wintermere, D.: Diffusion Plate Assay for Chloramphenicol and Aureomycin, J. Clin. Investigation **28**:940, 1949.

8. Personal communication to the authors from Parke, Davis & Company, Detroit.

The data in table 2 show that chloramphenicol penetrates into the vitreous humor from the blood stream. The concentrations are not quite as high as those found in the aqueous humor.

TABLE 1.—*Concentration of Chloramphenicol in Aqueous Humor Expressed in Micrograms per Cubic Centimeter, After Intravenous Administration in a Dose of 50 Mg. per Kilogram of Body Weight*

	Hours After Administration				
Rabbit Eye	½	1	2	4	6
1	30	5	0	0	5
2	22	5	0	0	5
3	28	5	0	5	7
4	22	11	0	5	7
5	..	14	..	..	..
6	..	17	..	..	..

TABLE 2.—*Concentration of Chloramphenicol in Vitreous Humor, Expressed in Micrograms per Cubic Centimeter, After Intravenous Administration in a Dose of 50 Mg. per Kilogram of Body Weight*

	Hours After Administration			
Rabbit Eye	1	2	4	6
1	5	0	0	5
2	5	5	0	5
3	5	0	5	7
4	5	10	5	7
5	7	..	7	..
6	7	..	..	..
7	7	..	..	..

TABLE 3.—*Concentration of Chloramphenicol in the Blood, Expressed in Micrograms per Cubic Centimeter, After Intravenous Administration in a Dose of 50 Mg. per Kilogram of Body Weight*

	Minutes After Administration						
Rabbit Eye	5	15	30	60	120	240	360
1	30.08	22.56	15.24	7.52	0	0	0
2	.....	26.0	.....	15.0	0	0	0
3	.....	.....	.....	0	0	0	..
4	.....	.....	.....	0	..	..	..

Table 3 reveals that the chloramphenicol reaches its peak level in the blood immediately after the intravenous injection and drops rapidly, so that practically none can be detected in the blood of the rabbit after two hours. This suggests that chloramphenicol appears to be fairly rapidly excreted or inactivated by the rabbit. The results presented in table 4 indicate that when larger doses are injected intravenously the blood level is higher and the drug does not disappear as rapidly. Moreover, the penetration into the aqueous humor and into the vitreous

humor is greater than that obtained with smaller concentrations administered intravenously. These data are illustrated in charts 1 and 2.

The peak of the concentration in the aqueous humor lags slightly behind the peak of the blood level, and the peak of the concentration in the vitreous humor lies behind that in the aqueous humor. Chloramphenicol disappears from the blood within two hours, whereas detectable amounts are still present in the aqueous humor for almost six hours. The vitreous humor also shows detectable concentrations for six hours. As with other substances intravenously administered, the concentration in the vitreous humor is always lower than the concentration in the aqueous humor, but the drug does penetrate readily into both the aqueous and the vitreous humor of a normal rabbit eye.

After intravenous administration of 50 mg. per kilogram of body weight, detectable concentrations were found in the cornea, aqueous humor, iris, vitreous humor, chorioretinal tissues, sclera, conjunctiva,

TABLE 4.—*Concentrations of Chloramphenicol, Expressed in Micrograms per Cubic Centimeter, After Intravenous Administration in a Dose of 150 Mg. per Kilogram of Body Weight*

	Minutes After Administration		
	5	45	120
Blood	180+	60	11
Aqueous humor	90	10	10
	..	22	17
Vitreous humor	50	10	12
	..	12	14

muscle and lacrimal gland. The level rapidly diminished, and at the end of four hours, after a single intravenous injection, only the aqueous humor, vitreous humor and chorioretinal tissues showed detectable amounts. When the intravenous injection was increased to 100 mg. per kilogram of body weight, higher levels were obtained in the cornea, aqueous humor, iris, vitreous humor, chorioretinal tissue, optic nerve, conjunctiva and muscle (table 5).

Oral Administration.—Detectable levels of chloramphenicol were demonstrable in the aqueous humor and in the vitreous humor for six hours after a single oral dose of 0.5 Gm. in rabbits weighing between 3 to 4 Kg. The concentrations obtained were not quite as high as most of those obtained after intravenous injections but were well maintained (table 6).

Alterations of the Normal Blood-Aqueous Barrier.—Table 7 lists the concentrations obtained in secondary aqueous humor. From these data, it is evident that the secondary aqueous contains slightly greater concentrations than those found in the primary aqueous. The concen-

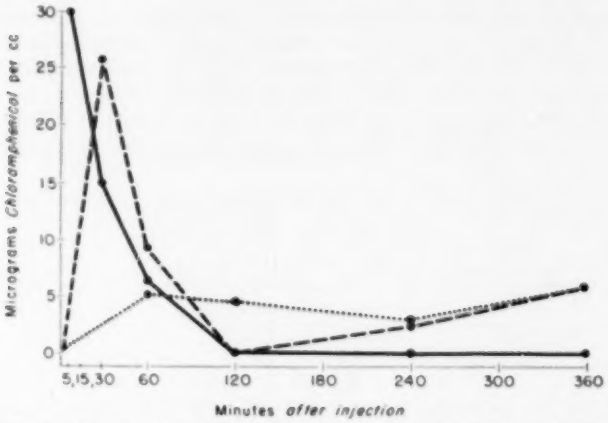

Chart 1.—Concentrations of chloramphenicol in the blood, aqueous and vitreous humor after intravenous injection of a solution of the drug in propylene glycol in a dose of 50 mg. per kilogram of body weight. Values for the blood are shown by the solid line; those for the aqueous humor, by a broken line, and those for the vitreous humor, by a line of dots.

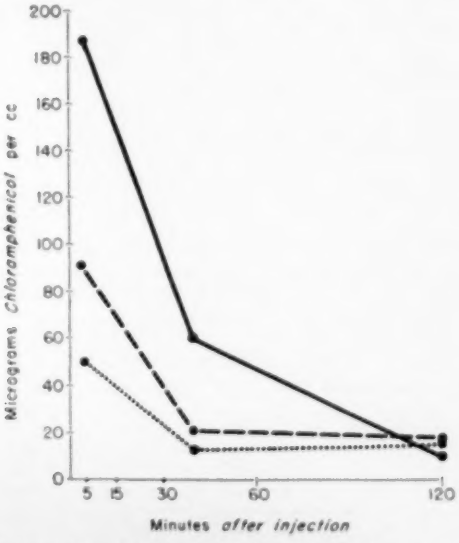

Chart 2.—Concentrations of chloramphenicol in the blood, aqueous humor and vitreous humor after intravenous injection of a solution in propylene glycol in a dose of 50 mg. per kilogram of body weight.

TABLE 5.—*Concentration of Chloramphenicol in Ocular Tissues or Fluids, Expressed in Micrograms per Gram of Tissue* or Micrograms per Cubic Centimeter of Fluid After Intravenous Injection of 50 or 100 Mg. per Kilogram of Body Weight*

Hours After Administration	1 50 Mg./Kg.	4 50 Mg./Kg.	1 100 Mg./Kg.
Cornea	5	0	10
Aqueous	9	3	15
Iris	10	0	11
Lens	0	0	0
Vitreous	5	2.5	12
Chorioretina	7	7	10
Sclera	7	0	7
Optic nerve	±	0	7
Conjunctiva	12	0	10
Muscle	7	0	8
Lacrimal gland	10	0	..

* Each tissue concentration represents the average for at least two specimens.

TABLE 6.—*Concentrations of Chloramphenicol, Expressed in Micrograms per Cubic Centimeter, After Oral Administration in a Dose of 0.5 Gm.*

	Hours After Administration			
	1	2	4	6
Blood	1	12	60	0
Aqueous humor	0	6	8	6
	0	1	5	8
	..	7	8	..
	..	..	8	..
Vitreous humor	0	8	8	5
	0	9	6	5

TABLE 7.—*Chloramphenicol Levels in the Primary and Secondary Aqueous Humor Forty-Five Minutes After Intravenous Administration in a Dose of 50 Mg. per Kilogram* of Body Weight*

Rabbit Eye	Concentration, Mg./Cc.	
	Primary Aqueous	Secondary Aqueous
1	11	18
2	14	17
3	17	15
4	5	22

* The eye used for determination of secondary aqueous humor had been previously tapped fifteen minutes after intravenous injection to remove the primary aqueous.

trations might have been higher if the blood level had not fallen so rapidly. Di-isopropyl fluorophosphate has been shown to increase the ability of fluorescein and of fibrin to penetrate into the anterior chamber.[9] However, previous instillation of di-isopropyl fluorophosphate did not alter the blood-aqueous barrier sufficiently to increase the intraocular penetration of chloramphenicol in the few eyes tested (table 2).

TABLE 8.—*Influence of Locally Instilled Di-Isopropyl Fluorophosphate (DFP),* 0.05 per Cent, on Penetration into Aqueous Humor of Intravenously Administered Chloramphenicol, 50 Mg. per Kilogram of Body Weight*

Hours After Administration			
1		2	
Normal Eye	Eye Treated with DFP	Normal Eye	Eye Treated with DFP
14	5	..	..
5	5	0	8

* Di-isopropyl fluorophosphate was instilled into the cul-de-sac twenty minutes prior to intravenous injection.

TABLE 9.—*Aqueous Humor Concentration, in Micrograms per Cubic Centimeter, After Drop Instillation of Chloramphenicol in Water (2.5 Mg./Cc.) or in Propylene Glycol (50 Mg./Cc.)* in Rabbit Eyes with Normal or with Abraded Corneas*

	Minutes After First Drop						
	60	75		90		150	
	Normal	Normal	Abraded	Normal	Abraded	Normal	Abraded
Aqueous solution	8	11	..	5	..	10	14
	10	14	..	10	..	10	19
	..	8	22	12	19	5	13
	..	5	22	..	..	5	5
Propylene glycol solution	5	5	14	0	..	..	..
	7	7	19	0	..	0	5
	0	7	14	5	24	5	5
	..	..	..	5	20	8	15

* One drop instilled every five minutes for six doses.

Local Administration.—Solutions: The data presented in table 9 disclose that chloramphenicol solution, either in water, 2.5 mg. per cubic centimeter, or in propylene glycol, 50 mg. per cubic centimeter, when

9. Aldrige, W. H.; Davson, H.; Dunphy, E. B., and Uhde, G. I.: The Effects of Di-Isopropyl Fluorophosphate Vapor on the Eye, Am. J. Ophth. **30**:1405, 1947. Leopold, I. H., and Comroe, J. H., Jr.: Effect of Diisopropyl Fluorophosphate ("DFP") on the Normal Eye, Arch. Ophth. **36**:17 (July) 1946. Scholz, R. O.: Studies in the Ocular Reaction of Rabbits to Di-Isopropyl Fluorophosphate, J. Pharmacol. & Exper. Therap. **88**:23, 1946. von Sallmann, L., and Dillon, B.: The Effect of Di-Isopropyl Fluorophosphate on the Capillaries of the Anterior Segment of the Eye in Rabbits, Am. J. Ophth. **30**:1244, 1947.

instilled as drops into the cul-de-sac of the rabbit eye with normal cornea, penetrated into the anterior chamber. Penetration was greater in the presence of a cornea which had been abraded. Penetration from the aqueous solution was slightly higher than that from the propylene glycol solution, although the concentration of chloramphenicol in the propylene glycol solution was greater.

TABLE 10.—*Aqueous Humor Concentration, in Micrograms per Cubic Centimeter, After Local Application of Ointment Containing 50 Mg. of Chloramphenicol per Gram of Base* to Normal and to Abraded Corneas*

	Minutes After Instillation							
	30		60		90		120	
	Normal	Abraded	Normal	Abraded	Normal	Abraded	Normal	Abraded
Petrolatum, U. S. P.	0	5	5	..	5	7	0	5
Hydrous wool fat–propylene glycol	7	23	10	46	..	..	5	28
	7	47	13	58	..	..	5	..
	..	..	..	..	..	..	5	37
	..	..	..	..	..	..	8	..

* The cul-de-sacs were thoroughly washed before the aqueous humor was withdrawn.

TABLE 11.—*Aqueous Humor Concentration, in Micrograms per Cubic Centimeter, After Subconjunctival Injection of 0.2 Cc. of Aqueous Solution of Chloramphenicol (2.5 Mg./Cc.) and of Propylene Glycol Solution (50 Mg./Cc.)*

Minutes After Administration				
30	60		120	
Aqueous Solution	Aqueous Solution	Propylene Glycol	Aqueous Solution	Propylene Glycol
5	9	65	5	90
6	5—	17	0	..
9	5—	..	5—	..
6	5—	..	5—	..

Ointments: Chloramphenicol penetrated from various ointment bases through the normal cornea into the aqueous humor. This can be seen from the data in table 10. Penetration was facilitated in the presence of the abraded cornea. The rate of penetration and the level reached were better from a hydrous wool fat–propylene glycol ointment base than from a petrolatum base.

Iontophoresis: Cathode iontophoresis produced an increased concentration of chloramphenicol in the anterior chamber (table 11). This method was used because of von Sallman's experience.[26] He demonstrated that cathode iontophoresis was much less damaging to the normal cornea than was anode iontophoresis. Perhaps higher concentrations might have been obtained in the anterior segment by the use

of anode iontophoresis, but we were interested in testing a method which might have practical value. Even with cathode iontophoresis, a few of the corneas stained after the application of 3 milliamperes of current for five minutes.

Chloramphenicol in aqueous solution when administered by subconjunctival injection produced definite irritation, which subsided rapidly. The concentrations obtained in the aqueous humor were not much greater than those obtained by local instillation and were not as high as those following iontophoresis (table 12). Propylene glycol preparations when administered subconjunctivally were exceedingly irritating and produced an intense reaction, which did not subside for several days. The levels obtained, however, were rather high.

Tolerance of Ocular Tissues.—In 6 rabbits standard corneal abrasions were produced in each eye. One eye was treated with propylene glycol solution alone, and the other eye, with chloramphenicol solution

TABLE 12.—*Aqueous Humor Concentration, After Iontophoresis for Five Minutes with Aqueous Solution in a Concentration of 2.5 Mg./Cc.**

Rabbit Eye	Concentration, Mg./Cc.
1	28
2	27
3	13
4	37
5	29

* Specimen from the anterior chamber was withdrawn fifteen minutes after onset of iontophoresis with cathode electrode on the eye.

in propylene glycol, 50 mg. per cubic centimeter. Drops were instilled at hourly intervals except at night, when the same concentration in hydrous wool fat U. S. P.–propylene glycol ointment base was instilled on one side and the ointment base alone on the other. No significant difference could be demonstrated in the rate of healing of the corneas. All eyes were healed by the fifth day. No scars or secondary infection developed in either series of eyes.

Chloramphenicol, in a concentration of 2.5 mg. per cubic centimeter of water, was injected into the anterior chamber of 6 rabbit eyes, approximately 0.1 cc. of this solution being injected. Immediately after the injection there were a mild pericorneal injection, flare in the anterior chamber and signs of iritis. In 2 eyes a fibrinous exudate was seen. Within twelve hours practically all signs had disappeared. Within twenty-four hours the eyes were white and quiet.

In 6 eyes intravitreal injections of 0.1 cc. of an aqueous solution of chloramphenicol, in a concentration of 2.5 mg. per cubic centimeter, were given. Injections were made in the area of the pars planum, and the needle was directed toward the center of the vitreous. The vitreous

was hazy for two and a half hours. The retina remained clear, without reaction except at the site of injection, where a small hole could be seen in the retina and choroid on inspection of the sectioned globe. There was mild conjunctival injection, most pronounced around the site of the needle puncture; this cleared in twenty-four to thirty-six hours. An excellent view of the fundus could be obtained at all times. Injection of 0.1 cc. of distilled water produced about the same changes. The only permanent damage occurred in the eyes in which the posterior surface of the lens was inadvertently struck by the injecting needle, in which case small posterior polar cataracts developed.

In another series of 6 rabbit eyes, 0.1 cc. of a solution of chloramphenicol in propylene glycol (50 mg. per cubic centimeter) was injected into the vitreous. The site of injection could be readily watched, and if the injection was made in the upper portion of the globe the entire injection mass could be seen to drop to the lower portion of the vitreous in the form of a large globule. Within three and a half hours crystal formations could be seen at the former site of the globule. There was no marked reaction of the vitreous around this well circumscribed injection mass. The crystals did not persist but within a few hours became an amorphous mass. The eye was white within five days. In 2 eyes a few small hemorrhages could be seen around the nerve head, but these also subsided. When 0.1 cc. of propylene glycol alone was injected, a large globular mass could be seen in the lower portion of the vitreous; this mass gradually disappeared during the next two days. In some rabbit eyes the grayish white, circumscribed mass of chloramphenicol in propylene glycol remained for four to five days before finally disappearing. In other eyes the mass remained for fourteen days, when the eyes were sectioned.

COMMENT

It is evident from these data that systemically administered chloramphenicol will penetrate readily into the normal eye. Almost all ocular tissues except the lens will show concentrations of this agent after intravenous administration. Oral administration of chloramphenicol is relatively free of toxic symptoms, and it has been demonstrated by these studies that when the drug is administered orally intraocular concentrations of chloramphenicol can be obtained.

These studies also reveal that chloramphenicol when locally instilled, either as drops of a solution or as an ointment, will penetrate the normal cornea. The rate and amount of penetration are greater in the presence of an abraded cornea. No serious irritating effects of chloramphenicol in aqueous solution could be demonstrated in the normal rabbit eye in concentrations of 2.5 mg. per cubic centimeter. Since the completion of these studies, the drug has been used in this concentration in human

eyes without any noticeable deleterious effect. Propylene glycol can be used as a vehicle when solutions containing higher concentrations of chloramphenicol are desired, as greater concentrations are not soluble in water. It does not appear that propylene glycol solutions will be required, as the drug penetrates readily from the aqueous preparations, and in what may prove to be adequate therapeutic concentrations. If higher concentrations in the cornea or the aqueous humor are desired, iontophoresis may be employed. Chloramphenicol will penetrate through the cornea into the aqueous humor from various ointment vehicles. The ointments used in these experiments are not ideal. Petrolatum gave lower concentrations than the hydrous wool fat U. S. P.–propylene glycol mixture, but this mixture was not sufficiently firm to make a satisfactory base. No deleterious effect of locally instilled chloramphenicol could be demonstrated on regeneration of corneal epithelium.

The drug was well tolerated by the anterior segment of the globe when injected into the anterior chamber in quantities of 0.1 cc. of a solution containing 2.5 mg. per cubic centimeter of water. It was readily tolerated by the vitreous humor and surrounding tissues when injected in the same concentration and quantity. Propylene glycol would be a poor vehicle for use in the vitreous humor, as chloramphenicol immediately precipitates out of this solution when coming in contact with the vitreous humor. However, even the precipitate produced no severe damage to the vitreous and surrounding tissues.

It is interesting to note that diisopropyl fluorophosphate did not sufficiently increase the permeability of the blood-aqueous barrier to allow greater concentrations of chloramphenicol in the aqueous humor after intravenous administration. However, paracentesis did increase the permeability of the blood-aqueous barrier, so that higher concentrations were obtained by this means. This result suggests that in the presence of severe inflammation higher concentrations of the chloramphenicol will be found in the intraocular tissues and fluids than in the normal eyes. All these observations indicate that chloramphenicol administered systemically, either intravenously or orally, can be expected to penetrate into the intraocular tissues and fluids in a concentration which should be suitable for the control of most infections resulting from agents sensitive to the drug. It probably will not prove necessary to resort to intraocular injections of the drug except in overwhelming infections.

Intraocular injection, particularly when intravitreal, is a heroic measure, although these, and other experimental and clinical studies, indicate that such injections can be tolerated when a proper dosage is maintained. Nevertheless, they should be used only when other measures will not be successful. Poor intraocular penetration of other

antibiotics made such injections necessary. The good intraocular penetration of chloramphenicol may reduce the necessity of intraocular, particularly intravitreal, injections.

Chloramphenicol has many advantages over other antibiotics available at this time. Like aureomycin, it is unusual in that it can be administered orally and, also, in that it is apparently effective in the treatment of infections caused by certain viruses and rickettsias, as well as bacteria. It has some advantages over aureomycin. This study has revealed that chloramphenicol will penetrate into the ocular tissues and fluids from the blood stream when administered orally. Studies by deRoetth [8a] and by Bellows, Richardson and Farmer [8b] indicated that systemically administered aureomycin in the usually recommended dose penetrated poorly, if at all, into the ocular fluid and tissues of the normal eye.

Approximately 50 per cent of all patients receiving aureomycin have had gastrointestinal irritation, the symptoms varying from anorexia to severe nausea, vomiting and diarrhea.[10] To date, practically no toxic symptoms have been noted after oral administration of chloramphenicol.[11]

Solutions of aureomycin for local use must be refrigerated, and they still lose their potency within forty-eight to seventy-two hours. A solution of chloramphenicol, 2.5 mg. per cubic centimeter in water, will, in our experience, maintain its potency for several weeks at room temperature. Thus, this drug can be ordered without the necessity of keeping it cool or of frequent renewals.

The field of activity is about the same for aureomycin and for chloramphenicol, although aureomycin appears to be more effective against gram-positive organisms. Good clinical results with chloramphenicol and aureomycin have been obtained in treatment of Rocky Mountain spotted fever, various types of typhus, primary atypical pneumonia, brucellosis, lymphogranuloma venereum and other infections.[12] Braley and Sanders [8b] and, more recently, Bellows and co-workers [8a] have reported on the local and local combined with systemic administration of aureomycin in treatment of ocular infections.

10. (*a*) Harris, H. J.: Aureomycin and Chloramphenicol in Brucellosis, J. A. M. A. **142**:161 (Jan. 21) 1950. (*b*) Zintel, H. A.: Clinical Use of Newer Antibiotics, Pennsylvania M. J. **53**:131, 1950.

11. (*a*) Ehrlich, J.; Bartz, Q. R.; Smith, R.; Joslyn, D. A., and Burkholder, P. R.: Chloromycetin, a New Antibiotic from a Soil Actinomycete, Science **106**:417, 1947. (*b*) Hewitt, W. L., and Williams, D., Jr.: Chloromycetin in the Treatment of Infections, New England J. Med. **242**:119, 1950. (*c*) Payne, E. H.: Present Status of Chloromycetin Therapy, New Orleans M. & S. J. **101**:597, 1949. (*d*) Smadel, J. E.: Clinical Use of the Antibiotic Chloramphenicol (Chloromycetin®), J. A. M. A. **142**:315 (Feb. 4) 1950. (*e*) Zintel.[10b]

12. Smadel.[11d] Zintel.[10b]

They successfully treated conjunctivitis due to staphylococci, pneumococci, Hemophilus influenzae, Hemophilus duplex, (Morax-Axenfeld bacillus) and Klebsiella pneumoniae. Our clinical experience with chloramphenicol is limited but suggests benefit in cases of conjunctivitis due to gram-negative organisms and of epidemic keratoconjunctivitis, as well as in those of other infections, but the cases are too few to permit any definite conclusions at present.

In most clinical cases to date in which treatment has been successful, the minimal effective blood concentration has been approximately 10 micrograms per cubic centimeter. This suggests that minimal effective tissue concentrations are less than 10 micrograms per cubic centimeter or gram of wet tissue. In vitro effective concentrations vary with the size of inoculum, the medium and the source of the organism, but for most of the gram-negative and for many gram-positive organisms effective inhibiting concentrations have been less than 3 micrograms per cubic centimeter.[13]

On the basis of these penetration studies, and of the accumulating clinical experience, it appears that chloramphenicol can be administered orally in doses of 3 to 6 Gm. daily. The initial dose should be approximately 3 Gm. This may be divided into 1 Gm., or 4 capsules (0.25 Gm.), every hour for three hours, or all 12 capsules may be given at one time; 0.5 Gm. every four hours can be given thereafter, or 0.25 Gm. every two hours. Locally, an aqueous solution of chloramphenicol containing 2.5 mg. per centimeter is safe and effective for administration as drops or by iontophoresis or intraocular injection. An ointment containing 50 mg. per gram of vehicle can be employed safely.

The present study demonstrates the ability of chloramphenicol to penetrate into the normal eye when systemically and locally administered. It appears to be a safe drug in treatment of ocular infections. Dosage schedules are suggested. The drug appears to have definite promise, but the final judgment as to where chloramphenicol will fit into the list of agents for treatment of ocular infection will depend on the results of adequate clinical experience.

One must keep in mind that susceptibility of micro-organisms to antibiotics varies greatly. The task of the physician in the future will not be simplified by the addition of new antibiotics. Actually, they increase his problems. The ophthalmologist, like other physicians, will have to maintain close connection with bacteriologic facilities. He will have to be informed not only on the organism responsible for the infection but also on the relative susceptibility of this organism to the various antibiotics available. He will also be influenced in his choice

13. Ehrlich and others.[11a] Smith, R. M.; Joslyn, D. A.; Gruhzit, O. M.; McLean, I. W., Jr.; Penner, M. A., and Ehrlich, J.: Chloromycetin: Biological Studies, J. Bact. **55**:425, 1948.

of drug by other factors, such as the ability to obtain and maintain intraocular concentrations, the sensitivity of the patient to the drug, the ease of administration and the cost.

SUMMARY

A single intravenous injection in rabbits of chloramphenicol solution in a concentration of 50 mg. per kilogram of body weight produced definite concentrations of the drug in the aqueous and vitreous humors and in the cornea, iris, chorioretinal tissue, sclera, optic nerve, conjunctiva, muscle and lacrimal gland.

The concentrations in these tissues were increased by raising the intravenous dose to 150 mg. per kilogram of body weight.

Secondary aqueous humor contained higher concentrations than the primary aqueous humor after systemic administration of chloramphenicol.

Local administration in the form of drops of a solution of chloramphenicol containing 2.5 mg. per cubic centimeter of water or 50 mg. per cubic centimeter of propylene glycol produced definite levels of the drug in the aqueous humor of a normal eye. Instillation of ointment preparations produced definite concentrations in the normal eye.

Higher concentrations were increased in the aqueous humor when the drug, in the form of drops or an ointment, was instilled into the cul-de-sac in the presence of an abraded cornea.

High concentrations of chloramphenicol were obtained in the aqueous humor of normal eyes after iontophoresis with an aqueous solution containing 2.5 mg. of chloramphenicol per cubic centimeter.

Subconjunctival injections of an aqueous solution of chloramphenicol containing 2.5 mg. per cubic centimeter produced detectable levels in the aqueous humor. Higher levels were obtained with solutions in propylene glycol in a concentration of 50 mg. per cubic centimeter injected subconjunctivally. However, the latter solution proved to be highly irritating.

An aqueous solution of chloramphenicol can be safely injected into the aqueous humor and the vitreous humor of the normal eye in concentrations of 2.5 mg. per cubic centimeter when 0.1 cc. of this solution is administered.

Chloramphenicol in concentrations of 50 mg. per cubic centimeter of propylene glycol showed no inhibitory influence on regeneration of corneal epithelium.

In a concentration of 2.5 mg. per cubic centimeter aqueous solution of chloramphenicol was stable at room temperature for one month.

On the basis of these studies, methods of administration and dosages for therapeutic use are suggested.

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CRANIOFACIAL DYSOSTOSIS (CROUZON'S DISEASE)

Report of Three Cases

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CRANIOFACIAL dysostosis, a rare deformity, produced by premature synostosis of certain craniofacial sutures, characteristically shows frontal bosses, prognathism, exophthalmos, exotropia, optic nerve atrophy and maxillary hypoplasia and, as will be shown, is a dominant hereditary character. Three cases of familial occurrence are described, and a preliminary report is given on a case in which the recommended surgical correction was made in early childhood.

CLASSIFICATION

Twenty-four divisions under the general condition of premature synostosis of the cranial sutures were found in the literature,[1] but the most popular and plausible classification, based on morphologic similarities, is that which follows:

Cranial stenoses (after Faber[2])

(*a*) Scaphocephaly, or boat skull: The sagittal suture closes prematurely, giving a long skull in the anteroposterior diameter.

(*b*) Brachycephaly, or broad skull: Premature closure of the coronal sutures produces a short (anteroposterior), but wide, skull.

(*c*) Acrocephaly (oxycephaly), or tower skull: As a result of premature closure of the coronal and sagittal sutures, the skull can only expand vertically.

(*d*) Craniofacial dysostosis, of Crouzon: Besides the involvement of the cranial sutures, there is involvement of the lower part of the face, and commonly it has a hereditary nature.

In the subsequent case reports, we are concerned with craniofacial dysostosis alone.

From the Department of Ophthalmology, University of Nebraska College of Medicine.

1. (*a*) Greig, D. M.: Edinburgh M. J. **33**:189, 1926. (*b*) Jacobi, A.: M. Rec. **45**:609, 1894.

2. (*a*) Faber, H. K.: California & West. Med. **22**:542, 1924. (*b*) Faber, H. K., and Towne, E. B.: Am. J. M. Sc. **173**:701, 1927

CHARACTERISTICS OF THE DISEASE

The cause of premature closure of the cranial or facial sutures is not known. Syphilis, rickets, birth trauma or disturbances of the glands of internal secretion apparently are not etiologic factors,[3] although all have been indicted.

Normally, continuous growth of the interstitial mesenchymal tissue between the bony margins of the centers of ossification prevents obliteration of the sutures. Loss of the sutures of the cranial vault by synostosis usually begins at about the age of 40, and the suture lines do not completely close until advanced age. However, premature synostosis may occur, the closure taking place before the brain has attained full growth. This condition seems to be due to a defect in the germ plasm producing abnormalities in the interstitial mesenchymal tissue, rather than to displaced centers of ossification. The condition is usually present at birth, but the deformity increases with the growth of the brain and in early life may easily be overlooked. Many of the milder forms of synostosis of cranial sutures are unrecognized. Perhaps this is fortunate, for these defects do not proceed to the development of cosmetic, visual or mental disturbances, and surgical therapy is therefore not justified.

The condition is characterized by certain changes in the bones of the skull. The skull shows bony changes in the region of the sagittal and coronal sutures, with resultant bosses, flattening or ridge formation. The face presents a hypoplastic maxilla and a high-arched palate. Typically the patients are mouth breathers. Prognathism is common.

The brain doubles in size at the end of the first seven months of life and triples in size at the end of two and one-half years.[2b] In the presence of a more or less nonexpandable skull, the growth of the brain results in increased intracranial pressure. This pressure may reach 500 mm. of water.[4] Headache may be a constant complaint up to the age of 8 years, when growth of the brain almost ceases. Convulsions and vomiting occasionally occur.[5] However, mental retardation is not a prominent feature.

The ocular changes play an important feature. Vision often is defective. The loss is usually due to optic nerve atrophy of the secondary type, following papilledema from increased intracranial pressure, but may be primary, due to a narrowed optic foramen or to pure mechanical stretching. The orbits are deformed, being shortened and having a

3. Park, E. A., and Powers, G. F.: Acrocephaly and Scaphocephaly with Symmetrically Distributed Malformations of Extremities: Study of So-Called "Acrocephalosyndactylism," Am. J. Dis. Child. **20**:235 (Oct.) 1920. Krause, A. C., and Buchanan, D. N.: Am. J. Ophth. **22**:140, 1939.

4. Bennett, A. E.; Keegan, J. J., and Hunt, H. B.: J. Nerv. & Ment. Dis. **84**:274, 1936.

5. King, J. E. J.: Ann. Surg. **115**:488, 1942.

more divergent axis, and the greater wing of the sphenoid bone may form the posterior, rather than the lateral, wall of the orbit. Exophthalmos secondary to the orbital edema and to the shallow depth of the orbits is common. These orbital changes often lead to both exotropia and exposure keratitis.

The roentgenologic picture is characterized by (1) absence of the suture lines in the fully developed cases; (2) digital impressions on the inner table of the skull from pressure by convolutions of the brain; (3) depression of the middle fossa, and (4) small paranasal sinuses.

TREATMENT

The inevitable complications of this condition are usually preventable by neurosurgical measures. Operation should be done as early as the disease is recognized, probably at the age of 6 months.[6] Corroboration may be obtained by roentgen examination; a family history of a similar condition; increased cerebrospinal fluid pressure, the usual precautions being observed to obviate herniations of the brain stem, and multiple ocular signs of the deformity. Linear craniectomy,[6] King's morcellation,[6] cranial uncapping or Keegan's mosaic craniectomy,[6] with or without the inclusion of tantalum foil,[1b] is performed to provide artificial suture lines, so that the skull may expand and save the patient from otherwise inevitable blindness (fig. 4 *C* and *D*). The surgical procedure of choice is probably not known; it may depend on which operator falls heir to the case.

The special problem of the ophthalmologist, after diagnosis, is the treatment of exotropia and of exposure keratitis from exophthalmos, if present. It is our belief that corrective muscle surgery should aim at overcorrection; otherwise, the results will not satisfy the operator or the patient. Treatment for imminent exposure keratitis is most easily and adequately carried out when lateral blepharoplasty is done (fig. 1 *A*).

A note of warning should be sounded, for surgical intervention in cases of microcephaly or mongolism placed the procedure in disrepute at one time.[1b] Differentiation from these conditions is necessary.

REPORT OF CASES

CASE 1.—*History.*—O. D., a white man aged 58 (second generation on the geneologic chart [fig. 5]), entered the University of Nebraska clinics, department of ophthalmology, with the chief complaint of progressive loss of vision extending over many years. The patient stated that in his early youth his eyes were prominent and divergent, the condition becoming progressively worse during his school years. The abnormal shape of his skull was noted at the same time. In 1913,

6. Mount, L. A.: New York State J. Med. **47**:20, 1947.

at the age of 22, the patient was seen by Dr. Harold Gifford Sr., at which time a lateral blepharoplasty was done on both eyes for the widened palpebral aperture in order to prevent exposure keratitis. He had had the usual diseases of childhood.

As shown in the geneologic chart (fig. 5), the patient's mother and father were reported as normal.

The patient had been a laborer all his life but was receiving assistance for the blind. He had 4 offspring, 2 of whom were similarly affected.

Physical Examination.—The patient was slightly asthenic, with obvious exotropia. He had a deformity of the skull and proptosis. Mentally he seemed slightly dull and phlegmatic but was cheerful and able to take commands readily. The skull was of the tower type, presenting increased width and flattened brow and occiput, with resultant shortened anteroposterior dimension and increased height. The temporal veins were prominent and pulsatile.

Ophthalmic examination revealed a visual acuity of 3/200 in each eye with correction. External examination showed proptosis of 23 and 24 mm. of the right and the left eye, respectively, as measured by the Hertel exophthalmometer. The palpebral apertures were shortened by the lateral blepharoplasty, so that the eyes had the appearance of protruding as on stalks (fig. 1 *A*). There was alternating exotropia of 30 degrees. The intraocular pressure measured 17 mm. of mercury (Schiøtz) in each eye. Ophthalmoscopic study showed typical secondary atrophy of the nerve head in both eyes. No papilledema was noted, but mild venous congestion was present. Other findings were not atypical for the age group involved.

The facial bones revealed a depressed infraorbital rim and underdeveloped maxillary ridge, and severe malocclusion, due to grade 3 (angle) prognathism, was present (fig. 1 *A*). The palate was high arched. A direct inguinal hernia was present on the right side.

Laboratory Examination.—The nonprotein nitrogen was normal. The urine was normal. The blood count showed 13.3 Gm. of hemoglobin per hundred cubic centimeters, 7,600 white blood cells and a normal differential count. The serologic reactions of the blood were negative.

Roentgenographic Examination.—The findings were compatible with craniofacial dysostosis (fig. 1 *B*).

CASE 2.—*History.*—F. D., a white man aged 25 a son of O.D. (third generation, fig. 5), entered the University of Nebraska clinics, department of ophthalmology, with the chief complaint of decreased vision in the right eye with deviation of this eye to the right. The patient stated that he had had the present condition all his life, with no change for the better or for the worse. He stated that he was also slightly "pop eyed," like his father and eldest son.

He had had measles and mumps in childhood and sinus trouble, with a recent submucous resection.

He had completed twelve grades in school and had encountered no scholastic difficulties. He had since worked as a laborer. Deferment in the armed forces was due to his eyes and to malocclusion. A vasectomy was done at the age of 23.

Physical Examination.—The patient was well developed and well nourished, apparently of the stated age, with obvious squint and facial deformity. He appeared alert, interested and intelligent.

The supraciliary ridge and frontal eminences were depressed. The skull was shortened in the anteroposterior diameter and lengthened vertically and laterally.

Vision with correction was 20/200 in the right eye and 20/25 in the left eye. External examination revealed normal palpebral apertures, but an exophthalmos of 21 and 22 mm. of the right and left eyes, respectively. There was right

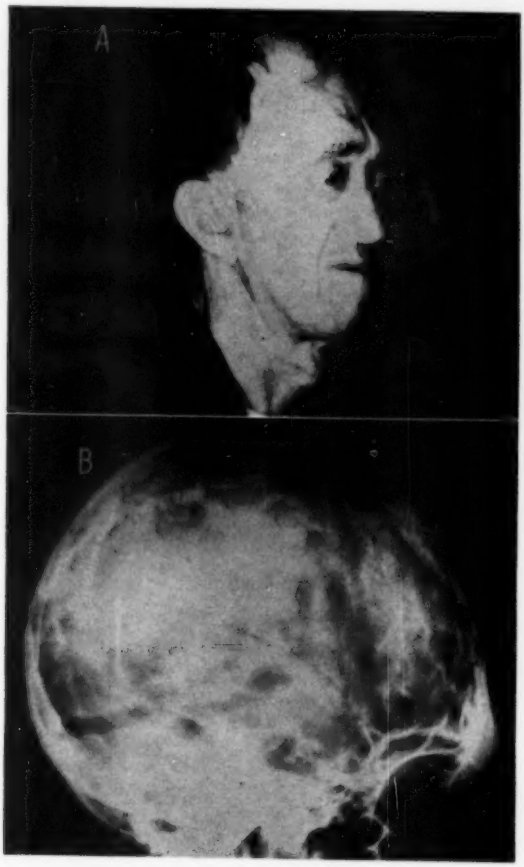

Fig. 1 (case 1).—*A*, prognathism, deformity of the skull and exophthalmos with lateral blepharoplasty. The eyes appear as though on stalks. The roentgenogram (*B*) shows typical findings.

exotropia of 40 degrees, which was concomitant. The pupillary reaction was normal, but sluggish. Examination of the fundi revealed secondary optic nerve atrophy of both eyes, with a low grade (1 D.) papilledema on the left.

The nose was deviated to the left. The right external naris was narrowed; a septal perforation was present; the mucosa was normal; the discharge was serous and slight.

There was prognathism of moderate degree. The palate was high and arched.

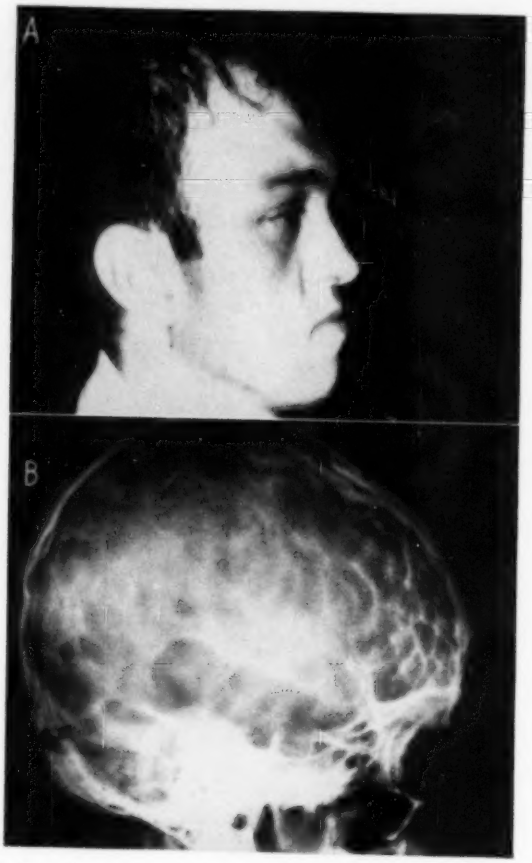

Fig. 2 (case 2).—*A*, prognathism and deformity of the skull. Exophthalmos was not marked in this patient, but exotropia (not shown) was present. *B*, typical roentgenographic findings in the skull.

The only other physical abnormalities were scoliosis to the right, of mild degree, and enlarged inguinal canals, without pulsation.

Roentgenographic Examination.—The findings were compatible with craniofacial dysostosis (fig. 2*B*).

Laboratory Studies.—The blood and urine were normal, and the serologic reactions were negative.

Operation.—A 5 mm. recession of the right lateral rectus muscle and a 5 mm. resection of the right medial rectus muscle were done. A dense, edematous

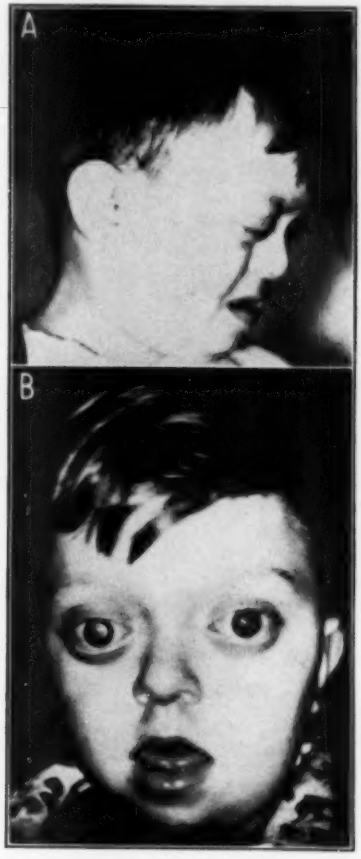

Fig. 3 (case 3).—Early prognathism, oral respiration and exophthalmos. A fundus reflex in the right eye simulates cataract.

Tenon's capsule was found. At a second operation the left lateral rectus was recessed 5 mm., with resulting measured exotropia of 10 degrees one month later, a condition cosmetically satisfactory.

CASE 3.—*History.*—S. D., a boy aged 4 years, the son of F. D. (fourth generation, fig. 5), was admitted with the chief complaints of protruding eyes, malformed skull and poor speech habits. The parents had noted these abnormalities during the latter portion of the first year of life, and the condition had seemed to progress.

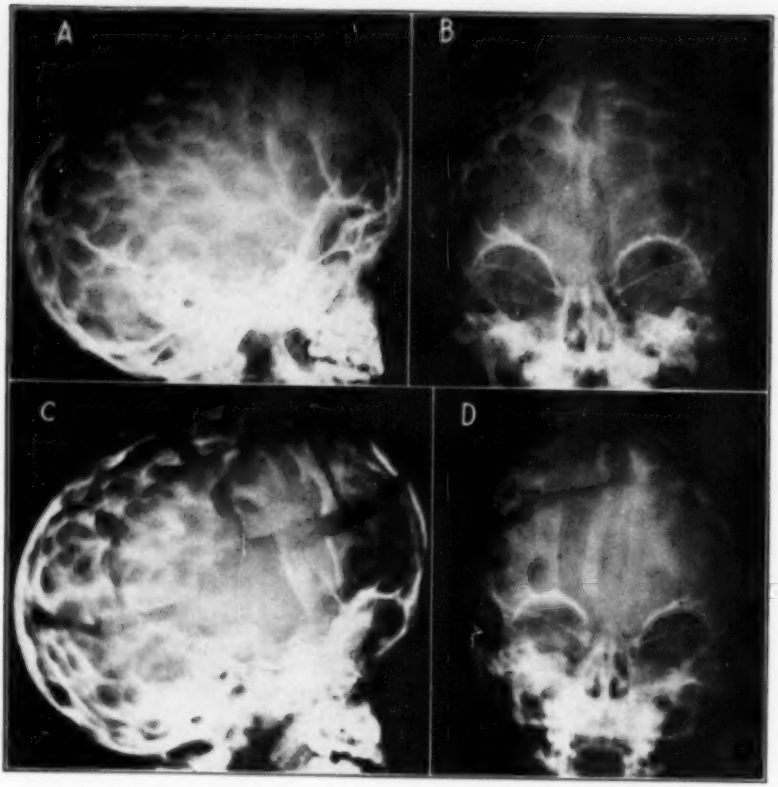

Fig. 4 (case 3).—*A* and *B*, typical findings in preoperative roentgenograms of the skull. *C* and *D*, roentgenograms of the skull after the first stage of mosaic craniectomy. Note the unilateral expansion of the skull outline in the antero-posterior view.

Developmental History.—The patient sat up at the age of 6 or 7 months, stood at the age of 1 year and walked at the age of 15 months. He first spoke at the age of 18 months, but the words were still poorly pronounced at the time of examination, and the patient was understood only by his parents. He was toilet trained at the age of 2 years. He had had a continuous cold each winter, for which tonsillectomy and adenoidectomy had been done one year previously.

Physical Examination.—The patient was a well developed and well nourished white boy, who appeared to be his stated age. He was alert and active and responded quickly. An obvious deformity of the skull was present.

In the region of the coronal suture was a ridge formation, about 0.5 cm. in height. There was flattening of the temporoparietal region. The temporal veins were prominent, especially with exertion.

The eyes were straight when in the primary position. External examination revealed palpebral apertures measuring 13 mm. in height in each eye, and bilateral exophthalmos, measuring 24 mm. The pupils were round, regular and equal and reacted to light and in accommodation, both directly and consensually. Ocular movements were full and conjugate. The cover test revealed exophoria of about 15 degrees. Ophthalmoscopic examination revealed only a mild degree of secondary atrophy, but definite papilledema could not be seen, perhaps because of lack of cooperation.

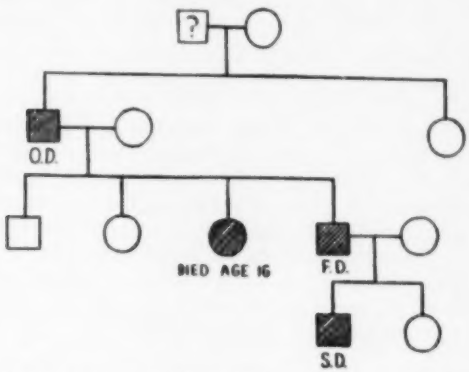

Fig. 5.—Genealogic chart showing inheritance of craniofacial dysostosis in a family of four generations.

The nose was normal.

Prognathism was present. The palate was high and arched. The nasopharynx was small in the lateral and the vertical diameter and appeared shortened in depth. The patient exhibited continuous oral respiration (fig. 3).

The remainder of the physical examination revealed normal development and function for a child of the age stated.

Laboratory Examination.—The results of routine laboratory tests were normal. Spinal puncture revealed a pressure of 230 mm. of water, with normal dynamics.

Operations.—The patient underwent two mosaic craniectomies on March 24 and April 4, 1949, respectively. The postoperative course was marred by a fall, with opening of the line of incision at the occiput; the wound was readily closed. Postoperative roentgenograms revealed an increase of 2 cm. in the lateral diameter of the skull as of April 18 (fig. 4).

The fourth member of the family with this condition, a girl in the third generation in the genealogic chart (fig. 5), was not examined by us, but was

reported by the family to exhibit abnormalities of the skull, face, eyes and jaw which were recognized as similar to those of the cases reported. This patient died of pneumonia at the age of 16 years.

HEREDITARY ASPECTS

According to the mendelian pattern, the genealogic chart for this family (fig. 5) should be interpreted as showing that the condition is a developed dominant character, with a heterozygous genetic pattern in the case of O. D. Thus, in his offspring this dominant feature was inherited in a 50:50 ratio, as would be anticipated. There was no sex linkage. It may be that one of the ancestral group in the first generation had the dominant character in such a minor degree that the condition was not recognized. The possibility of a homozygous recessive character accounting for the condition is not plausible in the light of the rarity of the condition and the necessity of the recessive gene's being present in both parents in each generation.

SUMMARY AND CONCLUSIONS

An attempt is made to classify the main groups of the cranial stenoses in a brief and usable manner. A short discussion of the etiology and the typical clinical and roentgenologic findings of craniofacial dysostosis is given. Emphasis is laid on the need of early diagnosis and neurosurgical treatment in order to forestall eventual catastrophe. Three case histories are included.

The 3 cases cited give proof of the hereditary nature and separate classification of this group of the cranial stenoses. The propriety of parenthood for afflicted persons is questionable.

CORNEAL RESPONSE TO EMETINE HYDROCHLORIDE

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DESPITE the use of ipecac powder and emetine hydrochloride in the treatment of various diseases, it is not generally appreciated that these chemicals may be locally irritating, and even severely toxic, to the ocular structures. In recent years evidence of a new interest in the potential danger of emetine hydrochloride has come to light in ophthalmologic literature.

Cushny [1] stated that emetine (ipecacuanha) may cause nausea and vomiting, muscular weakness, depression, increased secretion of saliva and of mucus by the glands of the throat and the respiratory passages, often perspiration and generally temporary acceleration of the pulse, and that it possesses a powerful local irritant action, which is severer in some persons than in others. In a subject who has an idiosyncrasy to emetine the smallest amount of the powdered drug will cause swelling and injection of the conjunctival and nasal mucous membranes. When applied to the skin, the drug may cause redness, itching and pustular eruption.

The comprehensive manual "Toxic Eye Hazards" [2] notes that ipecac (powder) may cause conjunctivitis with opacity of the cornea. McLaughlin [3] and Carpenter and Smyth [4] did not investigate the reactions of the human and rabbit corneas to emetine hydrochloride, but Estable,[5] of Uruguay, and Fontana,[6] of Italy, have recently conducted experiments on rabbit eyes. Estable used solutions of various concen-

From the Brooklyn Eye and Ear Hospital and Long Island College of Medicine.

1. Cushny, A. R.: Pharmacology and Therapeutics, ed. 13, Philadelphia, Lea & Febiger, 1947, p. 717.

2. Toxic Eye Hazards; Publication 494, New York, National Society for the Prevention of Blindness, Inc., 1949, p. 71.

3. McLaughlin, R. S.: Chemical Burns of the Human Cornea, Am. J. Ophth. **29**:1355 (Nov.) 1946.

4. Carpenter, C. P., and Smyth, H. F., Jr.: Chemical Burns of the Rabbit Cornea, Am. J. Ophth. **29**:1363 (Nov.) 1946.

5. Estable, J. J.: Ocular Effect of Irritant Drugs, Am. J. Ophth. **31**:837 (July) 1948.

6. Fontana, G.: The Action of Emetine on the Cornea, Arch. ottal. **52**:113 (May-June) 1948; abstracted, Am. J. Ophth. **32**:1296 (Sept.) 1949.

trations, beginning with a 1:10,000 solution and increasing to a 1:50 solution. The milder solutions caused conjunctivitis, which increased in severity as the concentrations increased. He produced corneal lesions with a 1:500 preparation. Stronger solutions produced more serious keratitic reactions. Estable concluded that emetine hydrochloride has a powerful and irritating local effect on the eyes, that these reactions begin in the vascular and progress to the nonvascular structures and that the intensity and time of appearance of the irritating effect are related to the concentration of the solution and to the frequency of the application. Fontana, using solutions of 1 to 5 per cent, produced lesions ranging from diffuse nebular clouding to ulcerations. Most of the rabbit corneas reacted within forty-eight hours and returned to normal in about twelve days. Fontana stated the opinion that anaphylaxis played an important role.

REPORT OF A CASE

I have had the opportunity of treating severe ulcerative keratitis with secondary glaucoma due to emetine hydrochloride.

A white man aged 47, a maker of medicinal tablets, was mixing a preparation of emetine hydrochloride and lactose on March 1, 1947. He was fully aware of the toxic qualities of emetine hydrochloride and wore a face mask, which, however, did not cover the eyes. That night he noted that his eyes were painful and generally uncomfortable.

The following day he placed himself in the care of an ophthalmologist. On March 6 he requested me to accept his case. Examination of the right eye disclosed nothing pathologic, and the visual acuity of this eye was 20/20. The left eye presented moderate edema of the lids, photophobia and lacrimation. The cornea was almost entirely denuded of its epithelium except for an irregular ring 2 to 3 mm. wide at the limbus; there were numerous flat, gray keratic precipitates over the entire posterior surface of the cornea, which was edematous with a brown-gray, incomplete, broad ring of infiltration in the stroma. The anterior chamber was deep, and the pupil was well dilated, with no pronounced changes in the structure of the iris. The lens appeared clear, as was the vitreous body. Details of the fundus could not be ascertained.

Treatment consisted of atropine cycloplegia, hot applications every three hours, followed by instillations of 0.5 per cent tetracaine hydrochloride ointment, when necessary, to relieve pain; use of an eye patch; rest in bed, and administration of codeine sulfate by mouth. General physical examination revealed nothing pathologic; the urine was normal, and Kahn flocculation tests gave negative reactions.

Healing was exceedingly slow, and the patient suffered intensely at intervals of three to four hours. Foreign protein therapy helped to relieve the pain and appeared to control the early involvement of the anterior chamber. On March 25 he complained of a sharp pain in the left eye, which occurred during the night. Examination disclosed an unusual phenomenon in the presence of an irregular, vertical subepithelial hematoma, measuring about 2 by 5 mm., located just temporal to the edge of the remaining ulcer. The hematoma probably arose from new capillaries extending into the cornea at 2 o'clock. While I was arranging for a photograph, the hematoma absorbed completely.

Hydrosulphosol® (a preparation of calcium polysulfide, containing small amounts of calcium sulfide, thiosulfate, pentathionate and other inorganic sulfur compounds), 1 : 40 in castor oil, was now used but it did not hurry the healing process, which was discouragingly slow.

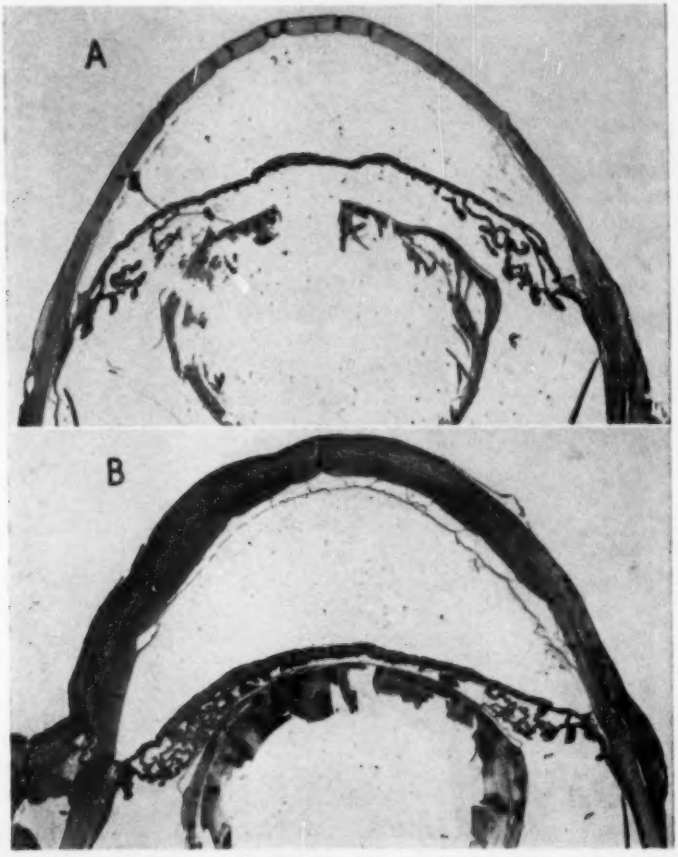

Fig. 1.—*A*, normal rabbit eye; *B*, rabbit eye showing reaction to emetine hydrochloride.

About the middle of April, when the ulcer was almost healed, during continued use of cycloplegia and foreign protein therapy, the intraocular tension started a slow rise. A 10 per cent solution of phenylephrine hydrochloride (neo-synephrin® hydrochloride) instilled daily helped to control the tension for a few weeks, but this medication became ineffective and a paracentesis was performed. The resulting

improvement was most gratifying, objectively and subjectively. The tension remained normal thereafter, and the ulcer closed completely within two weeks after the paracentesis.

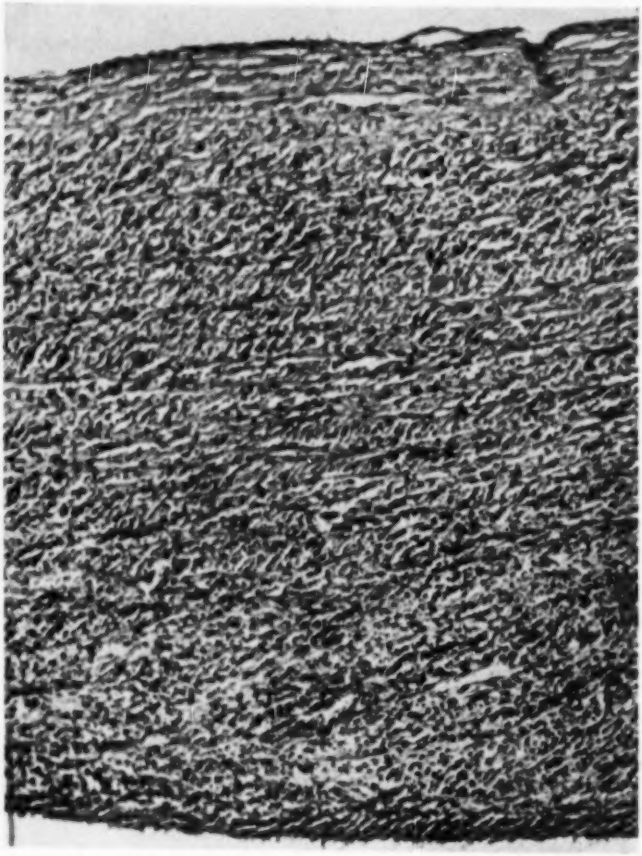

Fig. 2.—High magnification of the cornea shown in figure 1 *B*.

Considerable vascularization of the superficial stroma had taken place, together with dense scarification of the lower third of the cornea. The upper two thirds had a nebulous haze.

By the end of September 1947 visual acuity was 20/200 in the left eye. The anterior chamber was deep, and the iris reacted normally. There was a good

fundus reflex, and some retinal details could be seen; nothing pathologic in the fundus was noted.

The patient was last examined on Aug. 27, 1949. At that time the scar in the left cornea had taken on brown pigmentation superficially. The pigment appeared to consist of minute particles beneath the epithelium. Numerous empty capillaries could be seen, while a number filled with blood cells occupied the lower portion of the scar.

A sample of the emetine-lactose mixture was secured and placed in the conjunctival sac of a rabbit. In about twenty-four hours acute conjunctivitis and keratitis resulted. Both eyes were enucleated on the seventh day and sectioned under the supervision of Dr. J. Arnold de Veer, who submitted the following pathologic report:

"Acute keratitis with superficial ulceration is present. Some iritis accompanies the process. Other parts of the eye show nothing except changes attributable to hyperemia" (figs. 1 and 2).

It is readily seen that emetine is a dangerously toxic drug to ocular tissues when direct contact occurs. An adequate emergency plan of treatment should be kept in mind, as early elimination of the irritant is highly essential in order to safeguard vision. McLaughlin[3] recommended débridement of the cornea after chemical burns to the eye.

EXPERIMENTAL DÉBRIDEMENT

First Series.—McLaughlin's technic was applied in a series of 5 rabbits, both corneas in each rabbit being dusted with pure emetine hydrochloride powder. The powder was allowed to remain in contact with the corneas for five, ten, fifteen, fifteen and twenty minutes, respectively. Then the epithelial débridement of each cornea was accomplished. The rabbits were observed at frequent intervals, and all survived except for the rabbit with the ten minute exposure; this animal died on the third day after exposure. A résumé of the progress in each rabbit follows.

Five Minute Exposure: Right eye: Recovery was uneventful, with a faint residual central nebula, in seven days.

Left eye: A large infected corneal ulcer was still active at the end of fourteen days.

Ten Minute Exposure: Right eye: The cornea was severely ulcerated when the rabbit died, on the third postexposure day.

Left eye: The cornea responded similarly to the cornea of the right eye.

Fifteen Minute Exposure (2 rabbits): Right eye: Recovery was uneventful, with no corneal scars, in eight days.

Left eye: The corneas became severely scarred and were not completely healed after twenty-one days.

Twenty Minute Exposure: Right eye: The cornea responded well and was healed, with a residual central nebula, within eight days.

Left eye: The cornea became severely ulcerated, and when finally healed it was covered by a dense vascularized leukoma.

Of the 5 rabbits (10 eyes), 4 corneas made satisfactory recoveries after the débridement.

Second Series.—As a further experiment, 5 additional rabbits were exposed similarly to pure emetine hydrochloride powder. However, in these rabbits the cornea of the right eye only was débrided, the cornea of the left eye being left covered by the emetine powder. The same time intervals were maintained as with the preceding series. At the expiration of thirteen days all the corneas had healed over and were free of any staining with fluorescein. A résumé of the final results in each rabbit follows:

Five Minute Exposure: The right eye had a central macula of 3 mm.

The left eye had a superior macula of 3 mm. and an inferior macula of 2 mm.

Ten Minute Exposure: The right eye had an H-shaped central macula. The left eye had a central macula of 4 mm.

Fifteen Minute Exposure (2 rabbits): All 4 corneas were essentially the same, with a generalized nebulous haze in the stroma.

Twenty Minute Exposure: Both corneas had dense scars almost covering their entire areas.

The second series of rabbit corneas responded poorly in general to the McLaughlin procedure. However, the slightly better results in some of the débrided eyes is evidence that there may be merit in the procedure.

As has been noted earlier in this article, emetine hydrochloride applied directly to the rabbit eye invariably caused a reaction, which varied in severity with the concentration of the chemical. When the powder was applied, the rabbit cornea reacted violently.

It may be concluded, therefore, that the débridement was of benefit in some of the eyes exposed to the emetine hydrochloride powder. One may be justified further in stating that such treatment in the human eye, with the better after-care that is possible, will produce an even higher percentage of favorable results.

SUMMARY

1. Attention is directed to the potential toxicity of ipecac powder and emetine hydrochloride to the eye when these substances are dusted or instilled into the conjunctival sac.

2. A case is reported illustrating the severe pathologic change and great loss of vision the chemical can induce.

3. In accordance with McLaughlin's recommendation, denudation is suggested as a therapeutic means to the production of a more satisfactory healing process.

Fox Medical Building (17).

THE 1/2000 FIELD IN CHIASMAL INTERFERENCE

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AND
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OF THE various levels in the visual pathways at which pathologic changes cause characteristic field defects, the chiasmal area is the one where field studies can give the most information as to the site and amount of interference. It is at this level, moreover, that electroencephalography and neurologic examination may show very little. Plain roentgenograms may or may not reveal changes in the sella turcica or the tuberculum sellae. Pneumoencephalography, while often informative, is an uncomfortable, and sometimes even a hazardous, procedure. It is certainly too drastic a procedure for frequent follow-up studies, nor would it show the small variations in chiasmal interference that visual fields reveal. The same is essentially true for arteriography. Ophthalmoscopic study alone is an unreliable and inexact indicator of small variations in interference, because the pallor of optic nerve atrophy may be slow in developing, difficult to differentiate from physiologic temporal pallor and often out of all proportion to the actual amount of damage to the nerve fibers.

Visual acuity as measured on the Snellen chart is in itself a late index of involvement of the central field as compared with involvement of the more peripheral portion of the 1/2000 field, which lies somewhere between the 10 and the 25 degree arc. Changes in the periphery of this 1/2000 field usually occur first and may continue to increase and spread toward the fixation area for a long time before actually interfering with fixation, on which Snellen visual acuity readings depend. Therefore, the visual field study is the most practical and reliable one in evaluating the extent of interference at the chiasm for purposes of roentgen treatment or surgical intervention. The field changes, whether increasing or decreasing, are used for diagnosis and prognosis, as well as indication for further therapy. If, in the course of radiation therapy the visual fields show improvement or lack of further involvement, the treatments may be safely continued. On the other hand, a sudden over-all encroachment on the entire field following the early treatments may signify edema around the chiasm resulting from the therapy, and the radiotherapist

Read before the New York Society for Clinical Ophthalmology, Jan. 9, 1950.

will usually stop or diminish the amount of treatment until the field returns to its previous status. If the field continues to decrease in size, however, radiation therapy may have to be interrupted and surgical intervention resorted to. These principles of treatment were described by Davidoff and Feiring.[1] It is obvious, therefore, that careful and frequent field studies must be made, especially during the early course of therapy. If postoperative radiation therapy is used, the visual fields are again used as a guide in treatment.

In addition to pituitary adenomas, causes of chiasmal interference for which such field studies are used are suprasellar meningioma, glioma of the optic nerve, aneurysm of the circle of Willis, craniopharyngioma and some rarer tumors. In all these conditions, the visual field studies will usually be the guiding index to the progress of the lesion, increased or decreased interference being the indicator.

From these facts, one can appreciate the importance of precision and accurate detail in evaluation of the visual fields in chiasmal interference from whatever cause.

As far back as the end of the nineteenth century, Bjerrum advocated the use of small visual angles in studying the fields of vision. In 1915, Walker[2] recognized the importance of using test objects of various sizes in evaluating bitemporal hemianopsia. At that time he stressed the importance of evaluating the degree of involvement in a defective field by finding out the size of test object which was still visible therein, and thus he helped to lay the groundwork for modern quantitative perimetry. Whereas he stressed the size of the test object as the determining factor in the field to be involved sooner or later, we are concerned more definitely with the actual arc degrees of field involved first and the subsequent order of involvement.

Traquair[3] described the field changes in chiasmal interference as being one of two types, scotomatous and nonscotomatous. In his description of the so-called scotomatous type, he stressed the fact that even before a distinct scotoma is found next to the fixation area, the 1/2000 field for white, the periphery of which reaches up to 10 degrees in some persons and as far as 25 degrees in others, is likely to show a temporal slant.[4] As a matter of fact, even in his description of the nonscotomatous type, he again stressed the early appearance of changes within the 30 degree circle, which lies just beyond the outer limits of

1. Davidoff, L. M., and Feiring, E. H.: Surgical Treatment of Tumors of the Pituitary Body, Am. J. Surg. **75**:99-136 (Jan.) 1948, pp. 99-136.

2. Walker, C. B.: A Contribution to the Study of Bitemporal Hemianopsia, Tr. Sect. Ophth., A. M. A., 1915, pp. 173-208.

3. Traquair, H. M.: An Introduction to Clinical Perimetry, ed. 5, St. Louis, C. V. Mosby Company, 1946.

4. Traquair,[3] p. 207.

the 1/2000 field and, therefore, again mentioned this isopter as a choice one for determination of early changes.[5] We are in agreement with both these observations and wish to enlarge on the value of the 1/2000 field as an aid in the study of chiasmal interference.

PRESENT INVESTIGATION

Since there is no recognized division where the "central" field ends and the "peripheral" field begins, we prefer to designate the area from 10 to 25 degrees as the "intermediate" field and thus give a name to an area which seems to show so strikingly the effect of chiasmal interference.

In using the term the 1/2000 field, we always mean the 1/2000 field for white. The problem was approached from four aspects: (1) incidence and time of involvement of the 1/2000 field as compared with these factors for other fields; (2) extent of involvement of the 1/2000 field as compared with that of the peripheral field; (3) comparison of the 1/2000 field with fields for color; (4) comparison of the 1/2000 field with central visual acuity as measured on the Snellen chart as an indication of central involvement.

Each of these aspects will be discussed separately and illustrated with studies of the visual field in 22 cases. This series actually represents a small fraction of the many cases in which we have made similar observations.

Incidence and Time of Involvement of the 1/2000 Field in Relation to Other Fields.—Since the peripheral field and the central field each represents a different part of the visual pathways, and all fibers representing both the peripheral and the central field pass through the chiasm, any and all parts of the visual field are liable to involvement. It is proper, therefore, to examine both the peripheral and the central field.

In our experience, however, the 1/2000 field was always found to be involved at least as early as, and usually before, the peripheral field. Often the 1/2000 field showed definite involvement when the peripheral field was normal. This observation is not new and is in keeping with Traquair's observation that the 1/2000 field showed the earliest changes in both the scotomatous and the nonscotomatous types of field defects of chiasmal interference. This point is illustrated in cases 4, 5, 20 and 21. Not only was the 1/2000 field involved earlier than the peripheral field in untreated patients, but when improvement had taken place, as with roentgen therapy or surgical intervention, whereas the peripheral field showed improvement, the 1/2000 field continued to present evidence of chiasmal interference. Such observations are illustrated in cases 4, 21, 20, 17 and 22. With further improvement the 1/2000 fields also began to fill out, but only after the peripheral field had filled out first. This sequence is best illustrated in case 22.

5. Traquair,[3] p. 211.

In 1915 Walker [9] recognized the fact that the peripheral field was more likely to recover first, whereas the field "in and around the region of the caecocentral area [was] decidedly backward in repair." Actually, this field "in and around the caecocentral area" lies in the temporal, or most vulnerable, portion of the intermediate field. Therefore, the 1/2000 field is the first to go with chiasmal interference and the last to return with successful therapy. Since it is the first to be affected, one can see how easily an early bitemporal hemianopsia may be over-

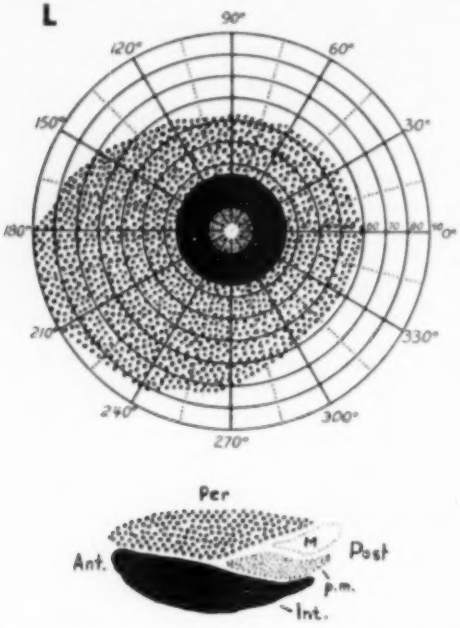

Fig. 1.—Concept of the dorsoventral relation of crossed and uncrossed fibers in the chiasm. The lower figure represents a sagittal section through the chiasm, and the upper figure, the corresponding representation in the visual field.

Per indicates peripheral fibers, representing the field peripheral to the 25 degree arc; *m*, macular fibers; *p. m.*, the perimacular fibers, representing the field from the macula to the 10 degree arc, and *int.*, the fibers representing the intermediate field (10 to 25 degrees). *Ant* indicates the anterior, and *post* the posterior, edge of the chiasm.

looked if only the peripheral fields are studied, and valuable time be lost in treatment.

Extent of Involvement of the 1/2000 Field as Compared with the Peripheral Field.—In all cases of chiasmal interference, with or without treatment, when the peripheral field was involved, the 1/2000 field was

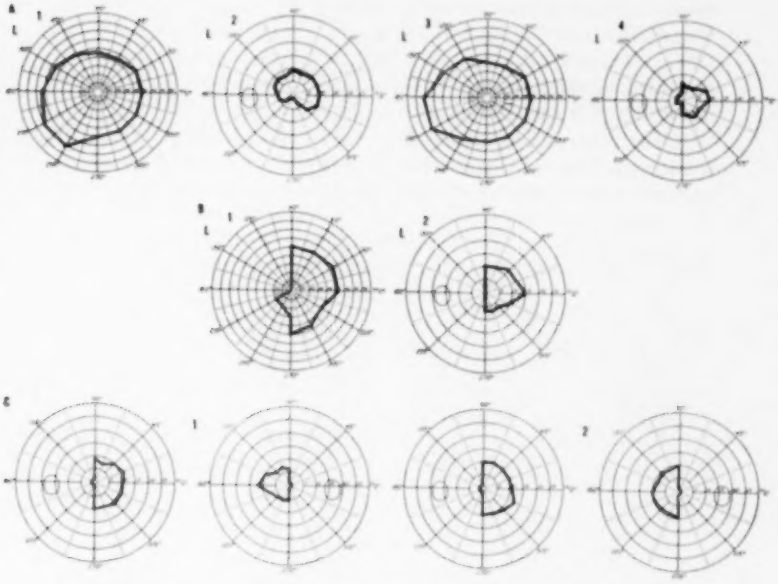

Fig. 2.—*A* (case 1), suprasellar meningioma in a woman aged 55. She had had several operations in the past few years, with complete loss of vision in the right eye, and had been last seen by us in 1933. She returned in March 1949, complaining of blurring of vision in the left eye.

1, peripheral field for 2/250 white on March 10, 1949, with visual acuity 20/30; *2*, 1/2000 field on March 16; *3*, peripheral field for 2/250 white, with no change in visual acuity, on April 14; *4*, 1/2000 field on April 14. While the final field is perhaps a little better below and nasally, there is definite temporal loss with hemianoptic features, indicating active chiasmal interference.

B (case 2), chromophobic adenoma of the pituitary gland in a man aged 50, who had been operated on a number of years before. Vision in the right eye was completely gone. He returned because vision in the left eye was failing.

1, peripheral field for 5/250 white, showing retention of some temporal field and of a nasal field, with visual acuity 15/100; *2*, 1/2000 field, showing complete temporal hemianopsia and beginning loss of the lower nasal quadrant, as well as involvement of the macular area to account for the loss of central vision.

C (case 3), chromophobic adenoma of the pituitary gland in a man aged 50 who was being treated with radiation therapy only.

1, 1/2000 field at onset of therapy. The right nasal field is definitely smaller than the left. *2*, 1/2000 field after three treatments. The filling out of the right nasal field is significant of improvement in this area.

Visual acuity remained 20/20 throughout all these tests, owing to the sparing of the macular area, even temporally. One can see that central vision alone, as measured on the Snellen chart, would fail to show the grave encroachment on central vision in a case such as this.

always involved at least as much, and generally more. This relation is illustrated in cases 6, 7, 14, 18, 17 and 21. Often, while the peripheral field showed no contractions, the 1/2000 field showed some depression of the upper temporal portion with hemianoptic features. These changes are observed in cases 1, 5, 8, 9, 10, 11, 12, 13, 17, 19, 20 and 21.

Often, when the peripheral field showed only incomplete temporal hemianopsia, the 1/2000 field showed complete temporal hemianopsia, or even involvement of the lower nasal quadrant as well, since the sequence of involvement of the 1/2000 field usually follows the same pattern as the peripheral defect, i. e., first the upper temporal, then the lower temporal, then the lower nasal and, finally, the upper nasal quadrant.

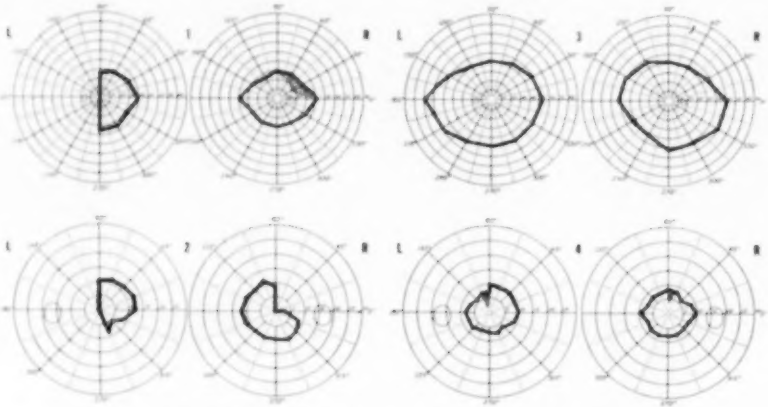

Fig. 3 (case 4).—Chromophobic adenoma of the pituitary in a man aged 40 with surgical removal of the tumor and postoperative radiation therapy.

1, preoperative peripheral fields for 1/330 white; visual acuity, 15/15 in the right eye and 15/40 in the left eye. *2*, 1/2000 fields (preoperative) taken at the same time as the peripheral fields in *1*. Note the intense hemianoptic feature in the right eye, not seen in the peripheral field. The left eye shows nasal involvement, not seen in the peripheral field. *3*, peripheral fields for 1/250 white three months after operation. These are normal in size and quality. *4*, 1/2000 fields after operation, recorded on the same day as those in *3*, and showing a remaining upper temporal defect in the left eye with a hemianoptic feature. In addition, both upper temporal fields show qualitative defects, brought out by "rapid comparisons."[6]

From the cases cited, it will be seen that the 1/2000 field is always involved as much as the peripheral field, and usually more.

Comparison of 1/2000 Field with Fields for Color.—We have found red a useful color to bring out qualitative differences within a given area of relatively defective central field.

Thus, if the 1/2000 field is present nasally, the patient may readily volunteer that the 5 mm. red test object looks orange in the lower nasal

portion and a deeper red in the upper nasal portion. Such readings are best within the 5 to 10 degree arc, readings farther out being rather poor for 5/2000 red.

However, if one relies on the red test object to demonstrate the actual extent of a particular isopter, certain technical difficulties arise. While the 5/2000 red stimulus may normally be recognized as "red" at 10 degrees, or in our experience more usually at 5 or 7 degrees, the recognition of the color is preceded by the awareness of a sphere as

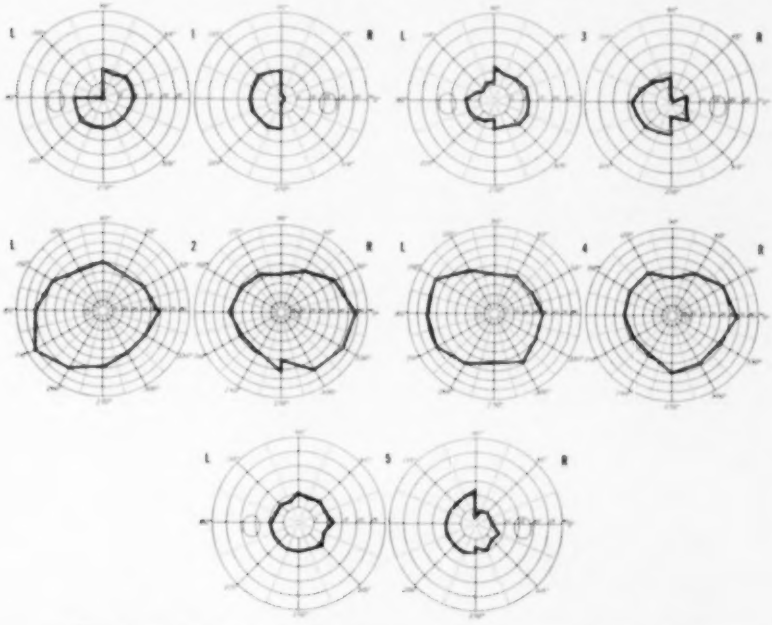

Fig. 4 (case 5).—Chromophobic adenoma in a woman aged 50 who had been given radiation therapy only.

1, 1/2000 fields on March 1, 1948, showing temporal loss in the right eye and loss in the left eye. The macula was encroached on in both eyes, with reduction of vision to 15/30—4 in the right eye and to 15/30 + 3 in the left eye. *2*, peripheral fields for 3/330 white on March 8, showing only a single questionable level difference. *3*, 1/2000 fields one week after radiation therapy was started. There is definite filling out of the lost temporal field with clearing of the macular areas and resultant improvement in central vision to 15/30 + 3 in the right eye and 15/20 + 3 in the left eye. *4*, peripheral fields for 2/250 white on April 3, which are not especially remarkable. *5*, 1/2000 fields on April 10, after six weeks of therapy, showing almost complete filling out of the fields of the left eye and notable improvement in the field of the right eye. Visual acuity was 15/20—4 in the right eye and 15/15—4 in the left eye. The visual acuity of the two eyes parallels the clearing of the macular areas in the 1/2000 field.

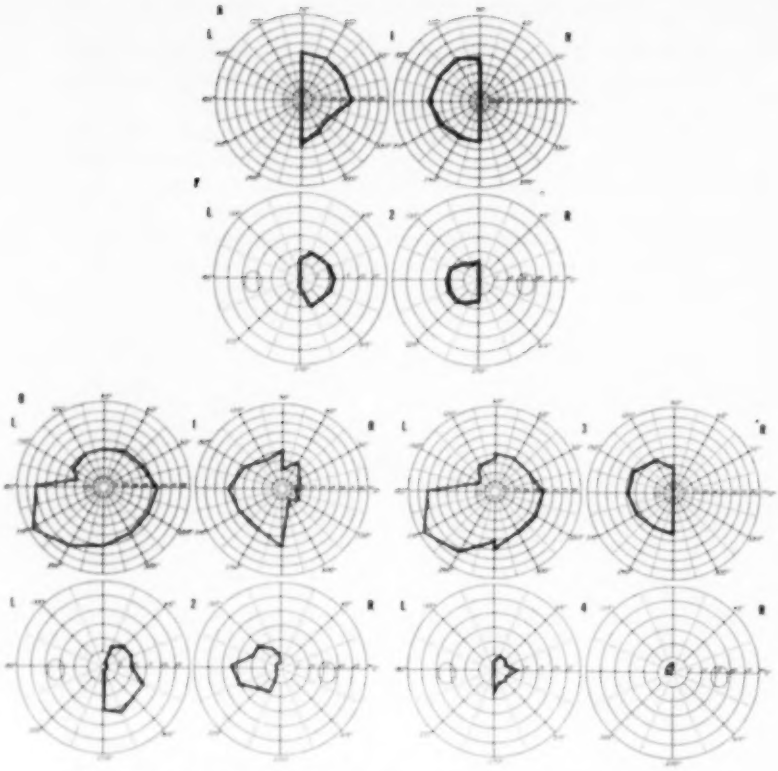

Fig. 5.—*A* (case 6), visual fields of white woman aged 46 who was receiving radiation therapy for tumor of the pituitary gland.

1, peripheral fields for 3/330 white, showing bitemporal hemianopsia. Visual acuity was 15/40 + 3 in the right eye and 15/20 in the left eye. *2*, 1/2000 fields, showing nasal involvement in the left eye near the vertical meridian. It is likely that the apparent severe involvement of the macular area is an error, the visual acuity being rather good for so much involvement.

B (case 7), chromophobic adenoma of the pituitary gland in a woman aged 35, who later showed evidence of Cushing's syndrome. The patient had had several operations and was receiving radiation therapy.

1, peripheral fields for 3/330 white on Sept. 22, 1947. Vision was 15/70 in each eye. *2*, 1/2000 fields at the same time, showing involvement of the nasal fields and macular areas. *3*, peripheral fields for 2/250 white on March 6, 1948. Vision was 15/100 in the right eye and 15/40 in the left eye. The remaining temporal field in the right eye had disappeared. *4*, 1/2000 fields on March 6, 1948. While the remaining nasal field in the left eye is smaller in over-all area than on September 22, the macular area is less involved and thus accounts for the improvement in central visual acuity. The right eye shows a definite diminution in the size of the remaining nasal field for 1/2000 but only a slight loss of visual acuity, since the loss has been in the 3 to 15 degree area, not immediately around the point of fixation. This case illustrates the inadequacy of visual acuity (Snellen) alone as an index of involvement of the central field.

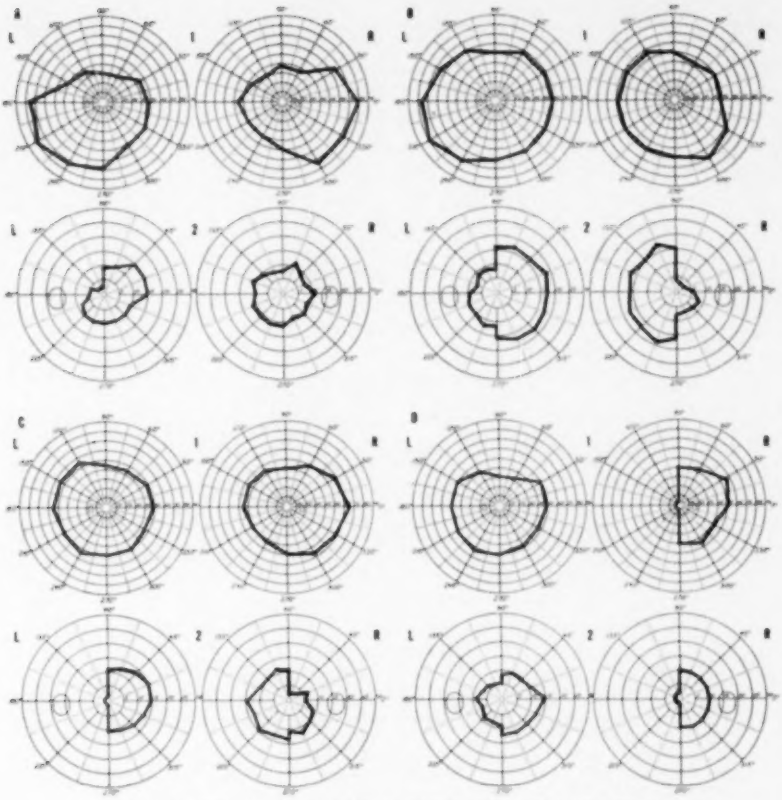

Fig. 6.—*A* (case 8), visual fields of elderly white man with long-standing acromegaly for which he had received radiation therapy.

1, peripheral fields for 3/330 white, which are not remarkable. *2*, 1/2000 fields, showing involvement in the left eye with loss in the upper temporal field and hemianoptic features. The proximity of the lost area to the point of fixation, with relative encroachment, probably accounts for the loss of vision in the left eye, which was 15/15 in the right eye and 15/20 in the left eye.

B (case 9), tumor of the pituitary gland in a white woman aged 27, for which she was receiving radiation therapy. Vision was 15/20—*2* in the right eye and 15/15—*2* in the left eye.

1, peripheral fields for 3/330 white, showing slight upper temporal depression in the right eye. *2*, 1/2000 fields, showing bitemporal involvement with hemianoptic features. The greater proximity of encroachment on the fixation area in the right eye may account for the slight difference of visual acuity in the two eyes.

C (case 10), chromophobic adenoma in a white woman aged 39, for which she was receiving radiation therapy.

1, peripheral fields for 3/330 white, which are a little small but show no hemianoptic features. Vision was 20/20 in the right eye and 20/30—*2* in the left eye. *2*, 1/2000 field, showing marked bitemporal hemianoptic involvement. Note the greater encroachment on the fixation area in the left eye, thus accounting for the slightly decreased central visual acuity.

D (case 11), history of radiation therapy in a man with chromophobic adenoma. *1*, peripheral fields for 3/330 white. Vision was 15/15 in each eye. *2*, 1/2000 fields showing residual effect in the left eye, not elicited in study of the peripheral fields. The complete sparing of the macular areas accounts for the normal central visual acuity.

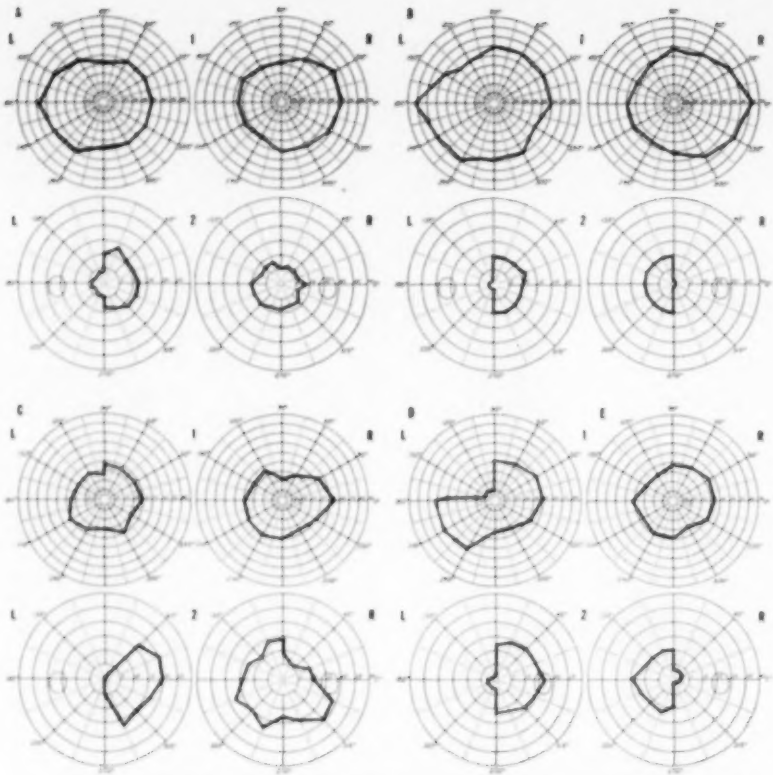

Fig. 7.—*A* (case 12), chromophobic adenoma in a man, for which he was receiving radiation therapy.

1, peripheral fields for 3/330 white, which are a little small but show no evidence of chiasmal interference. *2*, 1/2000 fields, showing persistence of loss in the temporal fields with hemianoptic feature in the field of the left eye.

B (case 13), craniopharyngioma in a boy aged 11, with return of peripheral field and central visual acuity after operation, but with persistence of bitemporal defect with 1/2000 white.

1, postoperative peripheral fields for 2/330 white; visual acuity, 15/15. *2*, 1/2000 fields taken at some time as the fields in *1*, showing persistence of bitemporal hemianopsia despite normal visual acuity and normal peripheral fields.

C (case 14), chromophobic adenoma in a woman, for which she was receiving radiation therapy.

1, peripheral fields for 1/330 white. These fields are a little small, but the only evidence of chiasmal interference is a small level difference and depression in the upper temporal quadrant of the left eye. *2*, 1/2000 fields taken at the same time as the fields in *1*. The field in the right eye shows a depression in the upper temporal quadrant with hemianoptic features. The 2/2000 field in the left eye shows complete temporal hemianopsia with involvement of the nasal field.

Note: The 2/2000 white test object was used here because the patient showed questionable recognition of the 1/2000 white test object. While the visual angle is larger, it may be used to good advantage in certain cases.

D (case 15), fields of a white man aged 32 who had been operated on for chromophobic adenoma and was receiving postoperative roentgen therapy. Vision was nil in the right eye and 15/20 in the left eye.

1, peripheral field for 1/330 white, showing loss in the upper temporal field. *2*, 1/2000 field, showing the greater involvement of the entire temporal field. The sparing of the macular area accounts for the good central visual acuity.

E (case 16), chromophobic adenoma in a man given roentgen therapy.

1, peripheral field for 1/330, which is small but shows no features of chiasmal interference. Vision was 15/15 in the right eye and nil in the left eye. *2*, 1/2000 field, showing pronounced temporal loss with hemianoptic features.

far out as 15 or 20 degrees, although at this arc the patient cannot tell the color very well. As the test object is brought in centrally, the patient will first call it white, then yellow, then orange and then a light red (at 5 to 10 degrees), but it will often not be recognized as bright red until it is brought within the 5 degree arc. These transitions of visualization are not sudden. Rather, there is a gradual change from one color to the other, and the patient will often be at a loss to give the exact point at which he really sees the object as true red. Besides, he will find it most difficult to use a single standard scale as a guide to what he calls "red" in the various meridians. The result will often be a very irregular field for a normal subject. We have, therefore, found the extent of the field for red a poor criterion to use for follow-up study

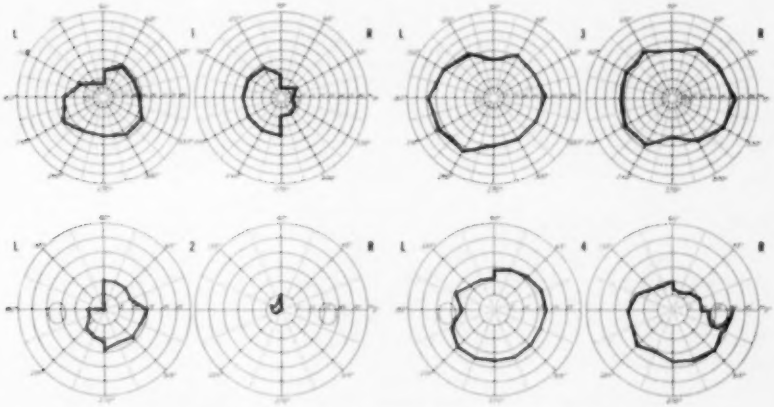

Fig. 8 (case 17).—Suprasellar cyst, probably craniopharyngioma, in a white woman aged 27.

1, preoperative peripheral fields for 1/330 white, showing bitemporal hemianoptic defects. Vision was 15/100 in the right eye and 15/15 in the left eye. *2*, preoperative fields, for 1/2000 white, showing much more extensive involvement. *3*, postoperative peripheral fields (three months) for 1/330 white, showing practically normal fields. *4*, postoperative fields for 1/2000 white, showing tremendous filling out, with persistence of the depression in the upper temporal quadrant in both eyes, with slight hemianoptic level differences and return of vision to 15/15.

and comparison. Traquair also stated that in the earliest stages of the scotomatous type of defect there may be a slight upper temporal slant for 1/2000 white, while color perception at this time is merely dimmed.[4] Even in his discussion of the nonscotomatous type of defect, he stated that whereas the 1/2000 white will show an upper temporal depression, it may or may not be possible to elicit corresponding changes for color with certainty.[5]

In the periphery of the field, we have found the red test object even more uncertain and, therefore, even less useful. Evans[6] also found color fields unsuitable for clinical work because of the inadequacy of normal standards as to extent of field, the lack of exact tints and in complete understanding of the normal mechanism of color vision. He cited the views of Lloyd, Traquair, Peter and Foster, all of whom were in general agreement as to the superiority of white test objects.

With the 1/2000 field, while there may be slight variations in the arc where the patient recognizes the test object, these variations are rarely more than 1 to 2 degrees, in contrast to the wide range found with the uncertain interpretation of colors.

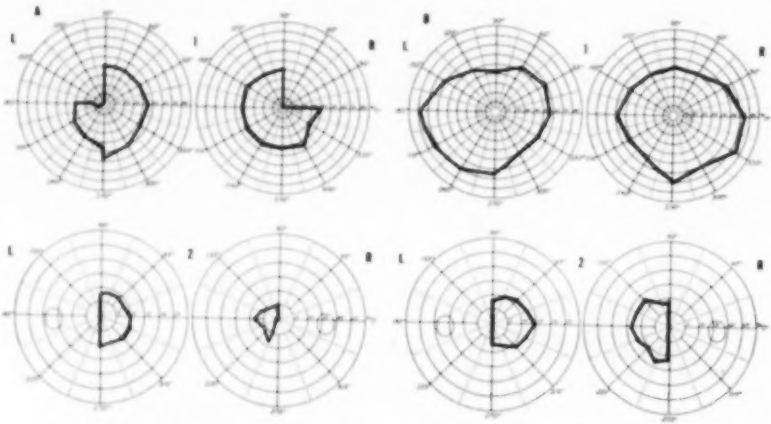

Fig. 9.—*A* (case 18), history of loss of vision due to chromophobic adenoma for two years in a woman aged 45.

1, peripheral fields for 1/250 white, showing bitemporal hemianoptic defects. Vision was 15/40 in the right eye and 15/20 in the left eye. *2*, 1/2000 fields, showing more extensive involvement, the greater involvement in the right eye accounting for the poorer vision in that eye. However, the relatively good visual acuity seems inconsistent with the great extent of macular involvement. It is likely that this was due to an error in technic.

B (case 19), mass lesion (probably metastatic) in the chiasmal area of an elderly man.

1, peripheral fields for 5/330 white, which are completely normal. Vision was 15/70 in the right eye and 15/200 in the left eye. *2*, 1/2000 fields, showing complete bitemporal hemianopsia, the involvement of the fixation area accounting for the diminution in central visual acuity.

For all these reasons, we feel that the test with 1/2000 white is much more accurate and satisfactory for evaluation and comparison of

6. Evans, J. N.: An Introduction to Clinical Scotometry, New Haven, Conn., Yale University Press, 1938, pp. 219-223.

the visual fields in cases of chiasmal interference than is the test with colored objects.

Moreover, even the qualitative differences of shades of red can be brought out with the 1/2000 white stimulus by the "rapid comparisons" method,[7] that is, by alternating rapidly the test object between the two areas of the field, when the patient will often say that it is clearer in one place than the other.

Comparison of the 1/2000 Field with Central Visual Acuity (Snellen) as Index of Interference.—Normal central visual acuity as measured on the Snellen chart is a function of the most central portion of the field,

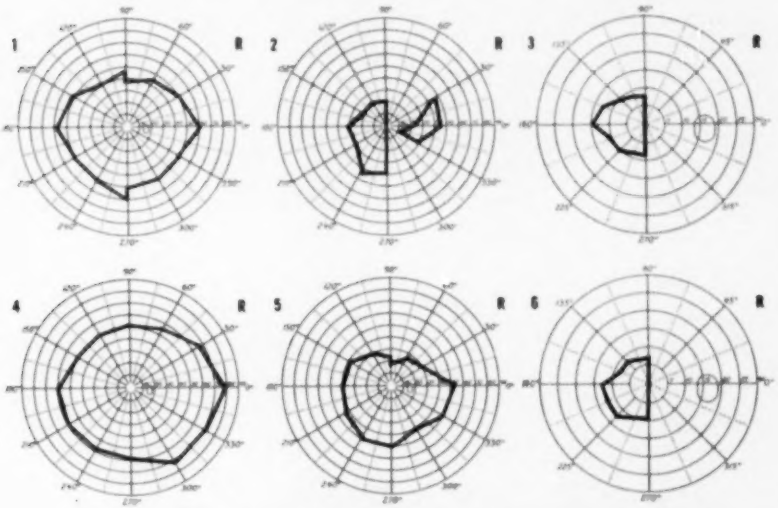

Fig. 10 (case 20).—Suprasellar meningioma in a woman aged 40. At the time of operation, the left eye had been completely blind for one year, and vision in the right eye was becoming blurred.

1, preoperative field for 5/330 white (vision 15/30); *2*, preoperative field for 1/330 white; *3*, preoperative field for 1/2000 white; *4*, postoperative field for 3/330 white (vision 15/20); *5*, postoperative field for 1/330 white; *6*, postoperative field for 1/2000 white.

In this case, while the peripheral fields showed definite improvement, the 1/2000 field continued to show the temporal hemianopsia.

in our opinion, probably within the 1 degree zone, or even more centrally. Therefore, a patient may continue to read 20/20 even though the 1/2000 field may be contracted to within the 1 degree arc or less

7. Chamlin, M.: Papilledema and Papillitis, Am. J. Ophth. **30**:741-747 (June) 1947.

temporally. To wait for a reduction in visual acuity as measured on the Snellen chart, therefore, means that one overlooks and ignores a period of increasing depression of the 1/2000 field until fixation is affected. Therefore, if one examines the 1/2000 field regularly, one will be able to detect any such encroachment on the fixation area proper, certainly long before the patient complains of visual loss. In this way, encroachment on central vision as measured on the Snellen chart can be foretold even before it occurs.

Once the fixation area is affected and central vision (Snellen) is diminished, the reading for central vision is often inconstant, showing wide fluctuations even within a few minutes. This is so because the patient can do his best reading by fixing a point far enough away from

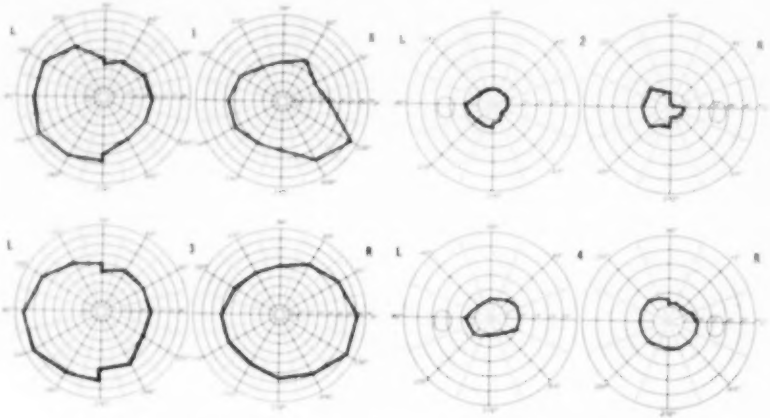

Fig. 11 (case 21).—Chromophobic adenoma in a man aged 45. The patient had never been aware of any visual disturbance. Vision was 20/20 in each eye. He was treated with radiation alone.

1, peripheral fields for 2/250 white before treatment was started. The level differences and slight nasal depression in the left eye are part of a right homonymous defect. The right eye shows a depression in the upper temporal field with no hemianoptic features. *2*, 1/2000 fields before therapy, showing right homonymous defects with hemianoptic features, as well as some depression of the left temporal field. *3*, fields for 2/250 white one month after the completion of fifteen sessions of radiation therapy. The peripheral field of the left eye shows only slight changes, and the peripheral field of the right eye has filled out. *4*, 1/2000 fields one month after completion of fifteen treatments, showing filling out of the nasal field and loss of the hemianoptic level difference. The small peripheral nasal defect filled out, and the greater 1/2000 nasal defect improved considerably.

the test letter that it is thrown into the most sensitive portion of the remaining paracentral visual field. Thus, if a patient with temporal hemianopsia attempts to read the large E at 3 or 4 feet (0.9 or 1.2 meters), he may have difficulty until he looks far enough temporal to the

letter that the E falls into his upper nasal field. Once such fixation is made, the patient may be able to read even 20/200, or perhaps even 20/70 if the immediate paracentral field is intact nasally. Therefore, it is evident that such readings are too often the result of fortuitous gazing on the part of the patient and cannot easily be relied on as an index of interference with the visual pathways for comparison from time to time. On the other hand, the 1/2000 field will be found to be much more constant in cases with such central involvement, even when fixation is a little difficult. Eccentricity of fixation may displace the 1/2000 field slightly, but will usually give a field of fairly uniform size on repeated examination. For the reasons mentioned, the extent and

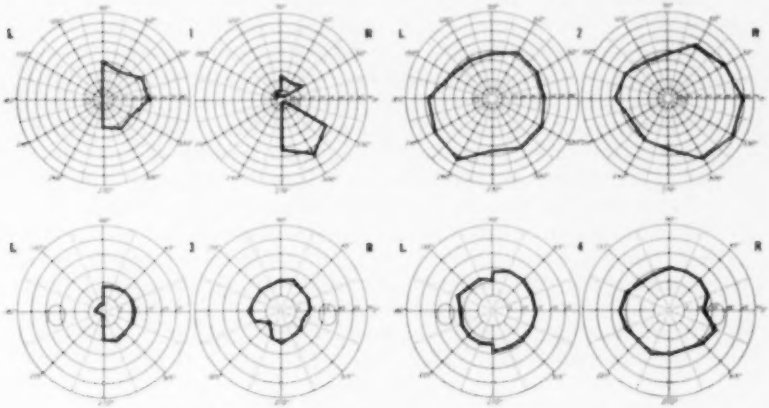

Fig. 12 (case 22).—Elderly man, with roentgenologic evidence of chiasmal interference and marked destruction of the sella turcica.

1, peripheral fields for 2.5/330 white (Dec. 16, 1946), showing pronounced left homonymous defect, as well as right temporal defect. Vision was 10/200 in the right eye and 15/70—2 in the left eye. *2*, peripheral fields for 2/330 white (April 1948), after several courses of radiation therapy. The fields are fairly full. Vision was 15/15—3 in the right eye and 15/15—3 in the left eye. *3*, 1/2000 fields taken at the same time as those in *2*, showing residual temporal hemianoptic defect in the left eye. *4*, 1/2000 fields in June 1949. No treatment was given between April 1948 and June 1949, but the 1/2000 fields, which in the left eye had continued to show a marked temporal hemianoptic defect, had gradually filled out to almost normal limits, but much more slowly than the peripheral fields, which were practically normal in April 1948.

contour of the 1/2000 field are more constant and a better index of the status of the central field than is the visual acuity (Snellen).

As a check on one's observations, increase or decrease in visual acuity should be accompanied with a corresponding change in the central field. Walker [2] made this point clear and warned against the recording of a normal field reaching into the fixation area when vision is down

approximately to 3/200. We feel that a much smaller loss than this, for example, one of from 20/20 to 20/40, or even to 20/30, should be demonstrable by changes in the central field near the fixation area. It is well to emphasize this point in view of the frequency with which one sees reports of severe changes in visual acuity with no changes in visual fields. Such reports are paradoxic and indicate incomplete study of the central field. As a matter of fact, the 1/2000 field should give a definite clue to the central visual acuity (Snellen); and when there is a difference in the acuity of two eyes which had equal vision before, the one with better vision shows a better 1/2000 field at the fixation area. This point is demonstrated in cases 4, 7, 8, 10, 14, 17 and 18. In these cases, one can see that when visual acuity (Snellen) is better in one eye than in the other, the better eye shows a 1/2000 field with less involvement of the fixation area. In some cases, while the fixation area is apparently spared for 1/2000 white, there is, nevertheless, loss of central visual acuity. This may be due to a relative defect encroaching on the fixation area which is not picked up by the examiner, but requiring a smaller test object to be demonstrated, or it may be due to an inconstancy in fixation.

In any event, central visual acuity as measured on the Snellen chart may be considered a rather late index of involvement of the central field and is preceded by much change in the intermediate field, or more peripheral part of the 1/2000 field. Such early changes long precede any subjective complaints and should be demonstrated and used to advantage for proper treatment, instead of waiting for involvement of the fixation area.

COMMENT

The frequency and extent of involvement of the 1/2000 field could probably be explained much better if one had more information on the exact distribution of the fibers in the optic chiasm. While Wilbrand and Saenger, Henschen and Roenne have described the distribution of macular fibers in the posterior chiasmal area, the explanation is not entirely clear. Even if their descriptions are accurate, one would still find difficulty in locating the fibers that convey the sensations from the intermediate, or 1/2000, isopter, that is, that portion of the field lying between 10 and 25 degrees. These fibers really represent perimacular retina rather than the macula, and it is they that show the earliest and most significant changes in chiasmal interference.

It is reasonable that these fibers occupy an anatomic position in the chiasm which makes them most vulnerable to mass pressure from below. Since the crossed fibers are usually the ones to be affected first, and the macular fibers occupy the posterior edge of the chiasm,[8] it may

8. Traquair,[3] p. 79.

be that the fibers representing this intermediate field (10 to 25 degrees) occupy the ventral surface of the chiasm, with the posterior third just in front of the crossed macular fibers representing the inner 10 degrees of field and the crossing macular fibers forming the posterior end of the chiasm. In this scheme, the peripheral fibers would occupy the dorsal aspect of the chiasm (fig. 1).

Such distribution of fibers in the ventral portion of the chiasm would account for the early involvement of the intermediate, or 1/2000, field. Therefore, as the mass extended upward, it would involve fibers representing more peripheral parts of the field, thus causing the "non-scotomatous" field defect. If it spread posteriorly, it would involve the crossing macular fibers at the posterior edge, thus accounting for the scotomatous type of field defects. On the basis of such a concept, therefore, a mass coming from below as a rather pedunculated growth and extending directly upward would cause a defect in the 1/2000 field, followed by a peripheral defect, but with preservation of central visual acuity. On the other hand, if the lesion developed a wide base and spread posteriorly, the involvement of intermediate field would be followed by involvement of the inner 10 degrees; and, finally, by encroachment on the crossing macular fibers, at the posterior edge, central vision (Snellen) would be affected, thus giving the so-called scotomatous type of defect, while the periphery might still be normal. Another factor that might be involved here is the so-called prefixation or postfixation of the chiasm, so that a prefixed chiasm would be more likely to involve the central field and a postfixed chiasm the peripheral field. However, the intermediate field would still be the first to be involved.

Such a concept of distribution of fibers would also account for the clinical observations made with recession of the mass. Thus, as the mass diminished in size, as a result either of surgical intervention or of roentgen therapy, the upper fibers, representing the peripheral field, would be relieved of pressure first, with the earlier return of peripheral vision. Furthermore, as the "spread" of mass pressure diminished from the posterior edge, the central visual acuity would return. The field from 10 to 25 degrees, however, having been exposed to pressure the longest, would continue to show signs of chiasmal interference the longest, even though these signs might be minimal,[9] such as the "level differences" and "qualitative differences" of temporal hemianopsia. These theoretic concepts agree closely with the clinical observation that this intermediate field does actually show temporal hemianoptic features longest, and often permanently. Furthermore, such a mechanical concept would do away with the rather illogical theory of greater vulnerability of certain

9. Chamlin, M.: Minimal Defects in Visual Field Studies, Arch. Ophth. **42**: 126-139 (Aug.) 1949.

fibers, even though more deeply situated, in a nerve on which pressure is being exerted from the outside, whereas the outer fibers are not affected so much.

While the theory of greater vulnerability or selectivity of the macular fibers is plausible in relation to inflammations or intoxications, such as optic and retrobulbar neuritis and toxic amblyopia, it is difficult to conceive of a mass pressing on the chiasm with little effect on the immediate fibers but with more effect on the inner ones. Therefore, by this mechanical logic and the sequence of clinical involvement, we feel that the fibers representing the intermediate field occupy the ventral surface of the chiasm, with the inner 10 degrees represented by fibers in the posterior area of this ventral surface, just in front of the crossing macular fibers at the thin posterior edge.

These concepts are offered as a reasonable explanation of the clinical observations made in cases of chiasmal interference.

SUMMARY AND CONCLUSIONS

The 1/2000 field is the earliest to show initial chiasmal interference, as well as extension of existing interference, and the last to lose evidence of such interference.

Even when a peripheral defect is present in a case of chiasmal interference, the 1/2000 field will always show at least as much, and usually much more, defect.

The 1/2000 field for white is much more accurate and reliable than any of the fields for colors in following the progress of chiasmal interference.

The 1/2000 field will show important evidence of increased or decreased chiasmal interference long before central visual acuity (Snellen) shows any change, and it serves as an index of what may be expected to happen to the central visual acuity in that case.

On the basis of these clinical observations, but with no corroborative anatomic studies, a concept of the vertical distribution of peripheral, intermediate and central fibers in the chiasm is offered, the term "intermediate field" being introduced for the area between 10 and 25 degrees.

In the search for early chiasmal interference or in following any phase of such interference, the study of the 1/2000 field is indispensable.

RETINOBLASTOMA

Analysis of Seventeen Autopsies

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DURING the past eighteen years, 17 autopsy reports on histologically proved cases of retinoblastoma have been collected in the institutions mentioned. Ten of the postmortem examinations were performed in the Memorial Hospital; 6 in the Presbyterian Hospital, New York, and 1 in the Children's Hospital, Philadelphia. Since this number constitutes an unusually large single series of autopsies in such cases, it was felt that an analysis would be of interest. Rados [1] stated that approximately 1,000 cases of retinoblastoma have been reported. In the review of the literature by Wintersteiner,[2] in 1897, and that of Wilson and Thomson,[3] in 1900, 61 autopsies were reported. Since 1900, approximately 24 additional cases with necropsy have been recorded. These figures indicate that postmortem studies are made in less than 10 per cent of the cases of death from retinoblastoma. Many of the autopsies are incomplete, and it is understandable that misconceptions have arisen regarding the extent and locations of metastases in this disease. The term retinoblastoma is used in this paper, since this is the one now generally accepted in the United States.

GENERAL STATISTICS

Incidence.—The incidence of retinoblastoma in cases of general ophthalmic diseases is variously estimated as between 0.001 and 0.053 per cent. Adam,[4] working in the university clinic in Berlin, found in the

This work has been supported by donations from the Blind Service Association, Chicago.

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1. Rados, A.: Occurrence of Glioma of Retina and Brain in Collateral Lines in Same Family, Arch. Ophth. **35**:1-12 (Jan.) 1946.

2. Wintersteiner, H.: Das Neuroepithelioma retinae: Eine anatomische und klinische Studie, Leipzig, Franz Deuticke, 1897.

3. Wilson, F. M., and Thomson, E. S.: Cases of Glioma Retinae and Brain Metastases, with Autopsy and Review of Literature, Arch. Ophth. **29**:91-100, 1900.

4. Adam, C.: Statistisches, klinisches und anatomisches über das Glioma retinae, Ztschr. f. Augenh. **25**:330-350, 1911.

period from 1890 to 1909, 47 cases of retinoblastoma among 275,000 cases of diseases of the eye, i. e., 1 in 5,832, or 0.01 per cent. Berrisford's [5] figures showed 1 case in 96,144 cases of diseases of the eye (0.001 per cent); Jaffe,[6] 1 in 10,000 (0.01 per cent); Thompson,[7] 13 in 24,500 cases (0.053 per cent), and Sisson,[8] 203 in 498,057 cases (0.04 per cent), while Krauss and Goldberg [9] reported 1 case of retinoblastoma in 5,000 cases (0.02 per cent) at the Wills Hospital and 1 in 3,232 cases (0.03 per cent) at St. Christopher's Hospital for Children. Few statistics are available on the incidence of this disease in Negroes. Cohen,[10] citing Calhoun,[11] gave an incidence of 1 in 49,036 cases (0.002 per cent) at the Grady Memorial Hospital, Atlanta, Ga. Since the Institute of Ophthalmology opened, there have been 31,546 admissions, of which 2 have been of Negroes with retinoblastoma, or 0.006 per cent.

Age.—By far the largest number of patients with retinoblastoma are seen by the third year of life, according to most statistics. Wintersteiner,[3] in a series of 467 patients, reported that 56.7 per cent were seen by the end of the second year, 74.5 per cent by the end of the third year and 87.8 per cent by the end of the fourth year. The oldest patient in this series was 16 years of age.

Berrisford [5] stated the belief that most cases are seen in patients under 2 years of age. Of the 142 cases reported from Moorfields by Lawford and Collins,[12] Marshall [13] and Owen,[14] 56 occurred before the thirteenth month and 26 during the second year, or 57.7 per cent in the first two years of life. In Adam's [4] series of patients, 93.6 per cent were under 4 years of age, and the oldest was 11 years, with an average age of 2.57 years. Thoeny [15] listed 80 per cent of cases as occurring before

5. Berrisford, P. D.: Statistical Notes on Glioma Retinae, with a Report on 41 Cases (from Moorfields), Roy. London Ophth. Hosp. Rep. **20**:296-331, 1916.

6. Jaffe, M.: Retinoblastoma: Report of a Case with Complete Observations at Autopsy, Arch. Ophth. **12**:319-324 (Sept.) 1934.

7. Thompson, J. L.: Glioma of the Retina, J. A. M. A. **31**:628-632 (Sept. 17) 1898.

8. Sisson, E. O.: Glioma of the Retina, Ophth. Rec. **15**:156-162, 1906.

9. Krauss, F., and Goldberg, H. G.: Glioma Retinae: Clinical and Histological Report of a Case, Ann. Ophth. **14**:628-633, 1905.

10. Cohen, M.: Unrecognized Retinoblastoma and Pseudoretinoblastoma, Arch. Ophth. **4**:368-373 (Sept.) 1930.

11. Calhoun, E. P., cited by Cohen.[10]

12. Lawford, J. B., and Collins, E. T.: Notes on Glioma Retinae, with a Report of 60 Cases, Roy. London Ophth. Hosp. Rep. **13**:12-37 1890.

13. Marshall, C. D.: Notes on Glioma Retinae, Roy. London Ophth. Hosp. Rep. **14**:456-477, 1897.

14. Owen, S. A.: Glioma Retinae, Roy. London Ophth. Hosp. Rep. **16**:323-360, 1905.

15. Thoeny, O. W.: Retinal Glioma, Southwestern Med. **23**:119-120, 1939.

the end of the third year, and Knapp [16] stated that 94 per cent occur before the age of 4 years. Verhoeff [17] reported a case of retinoblastoma, verified microscopically, in a man aged 48.

Sex.—There appears to be no particular predilection for persons of either sex. Individual reports may show a predominance of cases in one

TABLE 1.—*Distribution of Cases of Retinoblastoma According to Sex*

Author	Male	Female	Unknown	Total
Hirschberg, J.: Der Markschwamm der Netzhaut, Berlin, August Hirschwald, 1869	37	24	16	77
Vetsch, U.: Arch. Ophth. **12**: 43-62, 1883	11	11	9	22
von Lukowicz, M.: Beitrag zur Prognostik des glioma retinae, Inaug. Dissert., Halle, 1884	11	15	1	27
Knapp [16]	5	1	1	7
Lawford and Collins [12]	30	27	3	60
Marshall [10]	15	17	0	32
Wintersteiner [9]	221	208	0	429
Owen [14]	15	24	11	50
Adam [4]	30	17	0	47
Davenport, B. C.: Brit. J. Ophth. **10**: 474-478, 1926	16	11	0	27
	391	355	32	778
Present series	37	35	0	72
Totals	428	390	32	850

TABLE 2.—*Distribution of 759 Cases of Retinoblastoma According to Laterality*

Authority	Bilateral	Unilateral	Total	Percentage (bilateral)
Lawford and Collins [12]	12 (omitting 4 probable cases)	43	55	21.8
Marshall [10]	12 (includes 1 unknown)	20	32	37.5
Wintersteiner [9]	97	309	406	23.9
Hirschberg, J.: Der Markschwamm der Netzhaut, Berlin, August Hirschwald, 1869	14	46	60	23.3
Vetsch, U.: Arch. Ophth., **12**: 43-62, 1883.	1	21	22	4.5
Davenport, B. C.: Brit. J. Ophth., **10**: 474-478, 1926	5	22	27	18.5
McCrea, W. B. E.: Brit. J. Ophth., **27**: 259-273, 1943	3	9	12	25.0
Berrisford [5]	6	33	39	15.3
Owen [14]	4	31	35	11.4
Present series	50	18	72	77.7
Totals	210	549	759	27.6

or the other sex, but the combined reported statistics show only a slight preponderance of males (50.5 to 45.9 per cent). Table 1 is a compilation showing the sex incidence in 850 cases.

16. Knapp, A.: Bilateral Glioma: Report of Case Unsuccessfully Treated with Radium, Arch. Ophth. **49**:575-584, 1920.

17. Verhoeff, F. H.: Retinoblastoma: Report of a Case in a Man Aged 48, Arch. Ophth. **2**:643-650 (Dec.) 1929.

Eye Involved.—The two eyes are involved about equally. The chief difference of opinion is concerned with the relation of unilateral to bilateral occurrence. Of 759 reported cases, the tumor was bilateral in 210 cases, or 27.6 per cent. Of the 72 cases seen in this institution, the tumor was bilateral in 56, or 77.7 per cent. This is the highest figure reported, and it is undoubtedly due to the special program of treatment by radiation and surgery [18] in these cases of bilateral retinoblastoma.

Table 2 lists the larger reported series according to distribution of unilateral and bilateral cases.

AUTOPSY SERIES

Of the 17 cases comprising the autopsy series, 10 were of males and 7 of females. The right eye was involved in 9 cases; the left, in 3, and in 5 the tumor was bilateral. The average age of the patient when first seen was 2 years 11 months, the youngest patient being 9 months and the oldest 11 years. The average age at the onset of symptoms was 1 year 5 months. The average time of onset of the recurrence after the completion of treatment was three and one-half months. The average time of recurrence from the onset of symptoms was approximately two years and one month. The average time of death after the completion of treatment was seven months, the shortest being two months and the longest sixteen months. Fifteen of the patients were of the white race, and 2 were Negroes.

Roentgenologic Findings.—At the present time, in practically all cases, routine roentgenograms of the orbit and skull are taken. These are taken with the use of anesthesia if this is necessitated by the patient's age. The films are examined especially for the presence or absence of calcium in the tumor, changes in the optic foramens or orbital walls and signs of increased intracranial pressure. Pfeiffer [19] reported the diagnostic value of the presence of calcium, stating that in approximately 75 per cent of cases there is roentgenologic evidence of calcification in the tumor. In the present series, which began in 1929, roentgenograms were taken in only 8 of the 17 cases. Roentgenographic studies were omitted in the earlier cases, since their diagnostic value was not appreciated until later. In 4 of these 8 cases the preoperative films showed calcification.

18. Reese, A. B.; Merriam, George R., Jr., and Martin, H. E.: Treatment of Bilateral Retinoblastoma by Irradiation and Surgery: Report on 15-Year Results, Am. J. Ophth. **32**(2):175-190, 1949.

19. Pfeiffer, R. L.: Roentgenographic Diagnosis of Retinoblastoma, Arch. Ophth. **15**:811-821 (May) 1936.

In 1 case the right optic foramen was enlarged, but the left was normal. Autopsy revealed that the tumor had spread posteriorly along the right optic nerve, involved the chiasm and continued into the left optic nerve. In 3 other cases the optic foramens appeared normal roentgenographically; yet in each the optic nerve was involved at this level. Van der Hoeve,[20] in 1925, first described the enlargement of the foramen accompanying the invasion of the optic nerve and verified the roentgenologic findings by subsequent pathologic study. However, he seemed erroneously to have assumed that absence of roentgenographic signs is indicative of an uninvolved nerve, for he stated that in the last 3 cases of bilateral retinoblastoma which he had seen the optic foramens were normal, and in accordance with this the children had had no symptoms of intracranial involvement. Stuhl,[21] in 1931, reported a case, confirmed at operation, with intracranial spread along the optic nerve in which the roentgenograms showed, in addition to signs of increased intracranial pressure, unilateral enlargement of the optic canal.

In all suspected cases of retinoblastoma roentgenographic studies should certainly be made, but the absence of roentgenologic changes should not produce a false sense of security. The absence of calcium in the tumor does not exclude this type of neoplasm, nor does the absence of bony changes in the orbit and/or optic foramen preclude invasion of the bone or involvement of the posterior part of the nerve. Early invasion of bone does not reveal itself roentgenologically, and dissemination along the optic nerve may be widespread without ever having enlarged the optic nerve to the point of producing an increase in size of the canal.

Treatment.—The manner in which the 17 patients were treated is of interest, and, as would be anticipated in the case of a malignant neoplasm, the methods were numerous. They were as follows:

	No. of Cases
Enucleation	4
Irradiation followed by enucleation	2
Enucleation followed by irradiation	4
Enucleation (one eye); exenteration (other eye)	1
Enucleation (one eye); irradiation (other eye)	4
Enucleation followed by exenteration (one eye) and irradiation (other eye)	1
Enucleation, exenteration, irradiation (one eye)	1
Total	17

20. van der Hoeve, J.: Glioma Retinae, Trans. Ophth. Soc. **45**(1):256-266, 1925.

21. Stuhl, L.: Canal optique dilaté au cours d'un gliome de la rétine propagé au chiasma, Bull. et mém. Soc. de radiol. méd. de France **19**:30-31, 1931.

Location of Recurrence.—In the majority of cases the recurrence was first observed locally in the orbit, and the full extent of the disease was not appreciated until autopsy. This was the situation in 10 cases. In 3 others there was evidence of recurrent disease intracranially. In another 3 cases there was no recurrent disease in the orbit, but the first manifestation of a recurrence was a distant metastasis. In 1 case evidence of renewed activity of the tumor appeared in the fellow eye.

Manifestations.—Symptoms are understandably lacking in these young patients, since their age precludes an appreciation of their disease. Only 1 complained of pain, and this was due to the glaucoma produced by the tumor. Thus, pain, as in other forms of carcinoma, is not a frequent presenting symptom. The signs first noted by the parents were somewhat varied but can be classified under several general heads. These signs and their frequency are as follows:

	No. of Cases
Whitish or yellowish reflex in the pupillary area	14
Poor vision	6
Redness of the globe	5
Enlargement of the globe	3
Squint	
Divergent	1
Convergent	1
Head tilt	1
Dilatation of the pupil	1

Analysis of Autopsy Findings.—This analysis had certain objectives, the more important of which are as follows: (1) determination of the actual sites of metastatic spread and their relative frequency; (2) determination of the method of spread to the various sites; (3) estimation, as nearly as possible, of the probable cause of death, and (4) classification of the cases according to the areas involved.

In table 3 are listed the sites of metastasis.

SITES OF METASTASIS

Intracranial Cavity and Skull.—Analysis of these cases reveals some form of intracranial metastasis in 16, or 94.1 per cent. In 9 instances the dissemination occurred along the optic nerve; in 2 the intracranial cavity was invaded from the nose through the cribriform plate; in 4 the invasion was from the metastases of the skull, and in 1 instance the route of invasion is not apparent from the autopsy syllabus. In 9 cases, or 52.9 per cent, the leptomeninges and subarachnoid space were involved. In 7 of these 9 cases the invasion occurred from the affected optic nerve and chiasm. The meningeal involvement was diffuse, and the overlying dura was unaffected. In 1 case the invasion occurred when the disease in the nasal cavity eroded through the cribriform plate. The tumor

spread diffusely through the subarachnoid space. In 1 instance the meninges were involved locally by direct spread from metastatic areas in the calvaria. In 9 cases, or 52.9 per cent, there were metastatic areas in the bones of the skull. The inner surface of the calvaria was eroded in only 3 of these cases. In 2 of these 3 cases the dura alone was

TABLE 3.—*Sites of Metastasis of Retinoblastoma in 17 Cases*

Site	No. of Cases
Bones around orbit (6)	
Frontal	3
Zygoma	1
Maxilla	5
Sphenoid	4
Ethmoid	2
Palatine	1
Lacrimal	1
Invasion of the nose (3)	
Mandible (2) (1 bilateral)	
Sinuses (3)	
Maxillary	3 (1 bilateral)
Ethmoid	3 (2 bilateral)
Sphenoid	1
Oral cavity (2)	
Lymph nodes (8)	
Submaxillary	1
Cervical	3 (1 bilateral)
Hilar	2 (1 bilateral)
Tracheobronchial	1 (bilateral)
Axillary	1 (bilateral)
Epitrochlear	1 (bilateral)
Retroperitoneal	3 (1 bilateral)
Pancreatic	1
Mesenteric	1
Inguinal	2 (bilateral)
Iliac	1 (bilateral)
Femoral	1 (bilateral)
Popliteal	1 (bilateral)
Intracranial structures (16)	
Intracranial portion of optic nerve	10
Chiasm	9
Thalamus	3
Dura	4
Arachnoid	9
Pia	9
Subarachnoid space	9
Ventricles	7
Third	7
Lateral	3
Fourth	2
Choroid plexus	2
Cerebral cortex	7
Pituitary gland	3
Cerebellum	4
Pons	2
Cranial nerves	3
Gasserian ganglion	1 (bilateral)
Spinal cord (4)	
Epidural	1
Dura	1
Subarachnoid space	3
Pia	3
Cord	2
Peripheral nerve roots	2
Cauda equina	2
Skull bones (9)	
Frontal	6
Temporal	4
Parietal	3
Occipital	3
Cribriform plate	3
Unspecified	5
Distant bones (9)	
Clavicle	3
Ribs	7 (6 bilateral)
Sternum	4
Humerus	5 (bilateral)
Ulna	3 (1 bilateral)
Radius	4 (3 bilateral)
Scapula	1 (bilateral)
Acromion	1 (bilateral)
Coracoid	1 (bilateral)
Vertebrae	8
Cervical	1
Thoracic	4
Lumbar	4
Sacrum	1
Pelvis	4
Ilium	4 (3 bilateral)
Ischium	2 (bilateral)
Pubis	2 (bilateral)
Femur	4 (2 bilateral)
Tibia	3 (1 bilateral)
Fibula	4 (1 bilateral)
Visceral organs (8)	
Liver	5
Kidney	3 (1 bilateral)
Testis	2 (bilateral)
Pancreas	1
Spleen	1
Ovary	1 (bilateral)
Uterus	1
Muscles (1)	
Paravertebral muscles in abdomen	2 (bilateral)
Great vessels (1)	
Abdominal aorta	1

involved, and in the third case the arachnoid and pia were locally invaded. This indicates that involvement of the pia-arachnoid and the subarachnoid space usually takes place by one mode of dissemination and invasion of the dura by another. The pia-arachnoid is oftenest invaded by spread from the involved optic nerve and chiasm, the details of which will be discussed later. The subarachnoid tumor may disseminate widely in this space or penetrate the underlying cortex, but it

was not observed to encroach on the overlying dura. Dural metastases, on the other hand, represent a direct spread from neoplastic areas in the calvaria. These metastases rarely penetrate deeper but may do so on occasion. The periosteum seems to be fairly effective in confining the metastatic areas in the calvaria within the bone.

In only 1 of the 9 cases with metastases in the calvaria did the lesions erode externally to involve the skin. The tendency seems to be for these

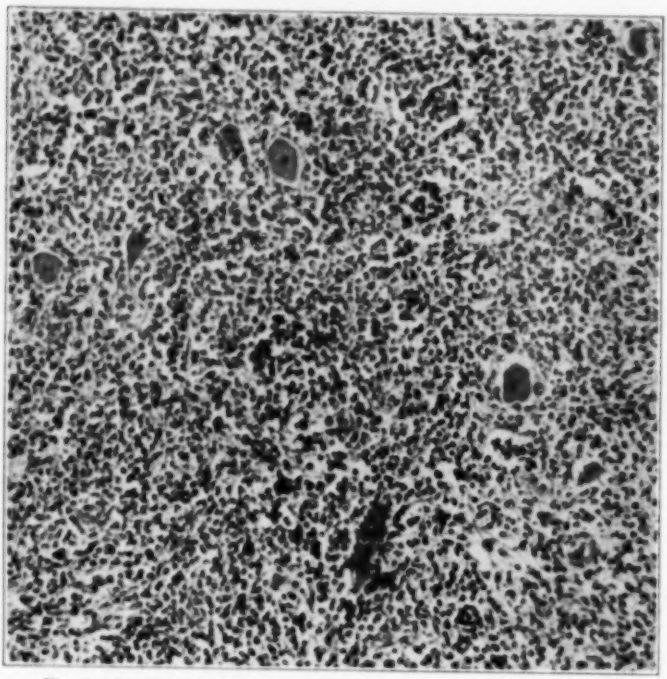

Fig. 1.—Section of gasserian ganglion invaded by retinoblastoma cells.

lesions to remain subperiosteal. Leptomeningeal invasion and invasion of the bones of the skull may coexist, but the routes of invasion are separate. The only exception to this occurs at the base of the skull when the cribriform plate is invaded directly from the nose. Then the continued inward erosion invades successively the dura, the leptomeninges and the cortex. This is a special situation, and even here, once the subarachnoid space is entered, the dura and the bones of the skull are not reinvaded in a retrograde manner.

When the leptomeninges are invaded, the tumor usually becomes widely disseminated in the subarachnoid space and thus comes to involve the sheaths of cranial nerves. This condition was found in 3 cases. The nerves themselves may be secondarily invaded. This is especially the case with the olfactory nerve, owing to its proximity to the chiasm and the intracranial portion of the optic nerves. In 1 instance the gasserian ganglions were invaded (fig. 1). As far as could be determined, no mention has been made in the previous literature of involvement of the

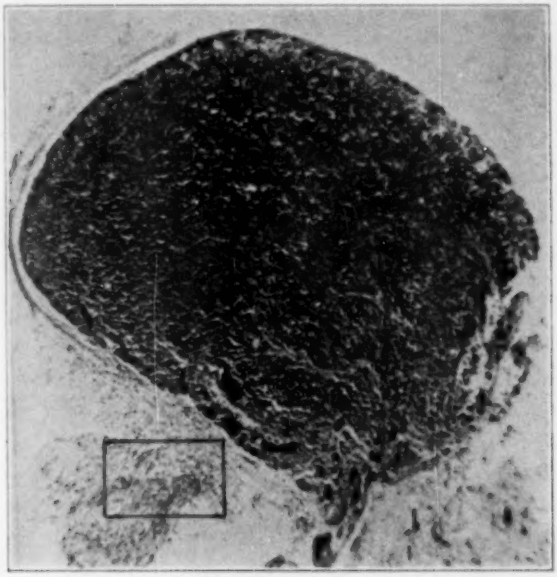

Fig. 2.—Pituitary gland, showing invasion of a portion of the capsule by retinoblastoma. The area outlined is shown in figure 3.

pituitary gland. The proximity of this structure to the optic chiasm makes it readily accessible, especially since leptomeningeal reflections form its capsule. In 3 instances the capsule was found to be involved (figs. 2 and 3).

The cerebral cortex was invaded in 7 cases; the cerebellum in 4 cases, and the brain stem itself, in 2 cases. Involvement of the brain substance may be the result of a direct spread from the subarachnoid space, usually penetrating along vascular channels, a direct invasion from the chiasm, or, as in 1 case, an invasion from the nose through the cribriform plate (fig. 4).

The optic nerve is important in the intracranial spread of the tumor and was found at autopsy to have been involved in 10 cases. It is most frequently invaded by direct spread from the optic disk, the tumor penetrating the openings in the lamina cribrosa along the central vessels and nerve bundles (fig. 5). The tumor continues in this fashion, spreading laterally as it progresses and eventually rupturing into the vaginal space. Rarely the vaginal sheath may be entered at the disk, as was seen in 2 cases. It has been stated that the nerve may be invaded from the orbit—

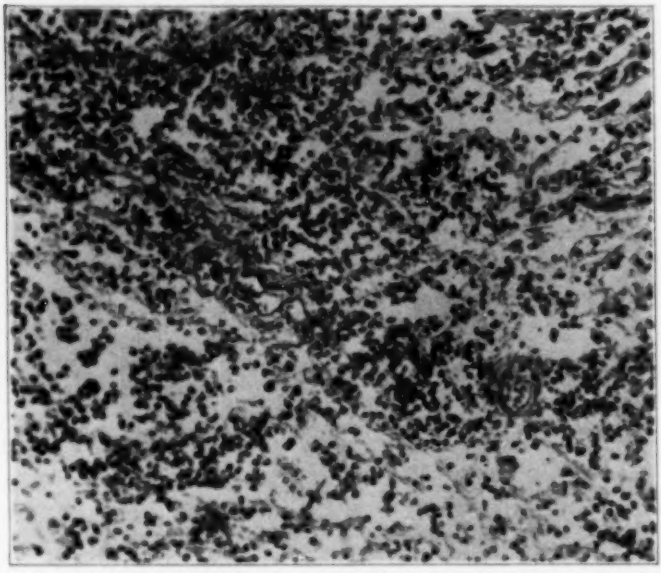

Fig. 3.—Higher magnification of the section outlined in figure 2, showing tumor cells in the capsule of the pituitary gland.

i.e., extrabulbar extension of the tumor, usually along an emissary vessel or nerve, and thence into the optic nerve. This was apparent in only 1 case. The optic nerve was invaded just at the disk and the rest of the nerve, including the site of operative section, was clear. The tumor spread out of the globe along the posterior emissaria and invaded the orbit. Autopsy revealed that the intracranial portion of the nerve was involved but that the chiasm was free of disease.

In serial sections of the orbital and intracranial portions of the nerve, the backward extension of the neoplasm is observed to be very irregular. In some sections the nerve itself is heavily invaded, and the sheaths are

Fig. 4.—Cerebrum and subarachnoid space, showing massive invasion of the latter and superficial cortical involvement.

Fig. 5.—Invasion of the choroid and optic nerve by retinoblastoma.

entirely free of disease. Other slides reveal the reverse, and still others show varying degrees of invasion of the entire nerve (figs. 6, 7 and 8). In only 1 of the cases in which sections were available was a nerve, the cut end of which was declared normal at the time of enucleation, seen to be invaded at autopsy. This exception has just been described. The desirability of obtaining a long nerve at the time of enucleation is obvious. This, and the effect of the status of the cut end of the optic nerve on the prognosis, have been stressed by Reese.[22]

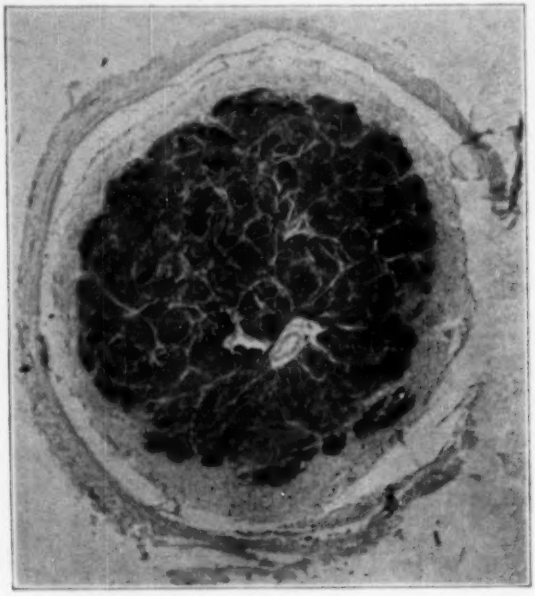

Fig. 6.—Section of optic nerve near the globe, showing massive involvement of the nerve proper with no invasion of the subarachnoid space.

In the nerve proper, the tumor spreads along the nerve bundles, and groups of neoplastic cells are seen to be separated by compressed trabecular fibers and atrophic nerve fibers. The tumor may invade the subdural space, but much more commonly it is observed in the subarachnoid space, where the spread is considerably more rapid than in the nerve itself. Once the sheaths have been entered, the neoplasm may continue

22. Reese, A. B.: Extension of Glioma (Retinoblastoma) into the Optic Nerve. Arch. Ophth. **5**:269-271 (Feb.) 1931; Invasion of the Optic Nerve by Retinoblastoma, ibid. **40**:553-557 (Nov.) 1948.

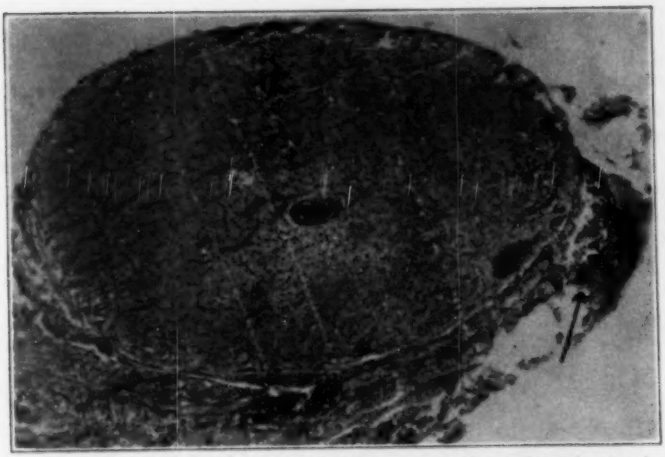

Fig. 7.—Section of the optic nerve about 10 mm. posterior to the globe, showing patchy invasion of the sheaths and vaginal space with only superficial involvement of the nerve proper.

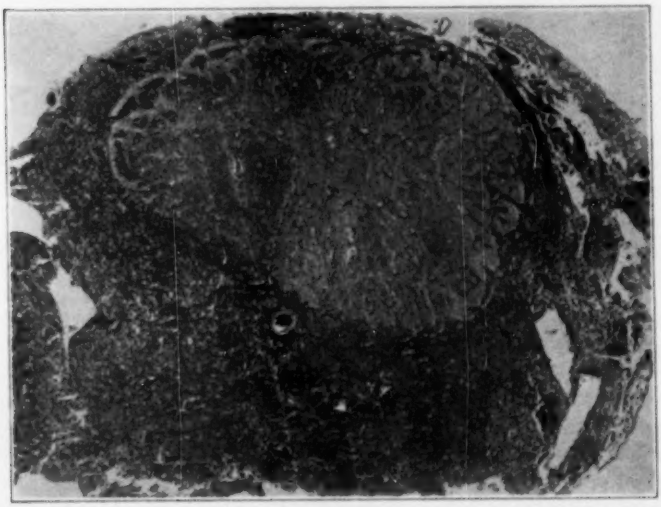

Fig. 8.—Section of the intracranial portion of the optic nerve, showing extensive involvement of the subarachnoid space and superficial invasion of the nerve proper.

in this plane for a varying distance and then reenter the nerve proper. In 4 instances the disease spread to the opposite nerve through the chiasm. Once the opposite nerve was invaded, the cells remained in the subarachnoid space and were not seen to enter the nerve proper. In 1 of these 4 cases the tumor extended to the opposite globe and invaded the sclera.

The intracranial portion of the optic nerve was observed to be invaded at autopsy in 10 cases. In 6 of these, the optic nerve showed invasion near the globe and in 5 at the site of operative section of the

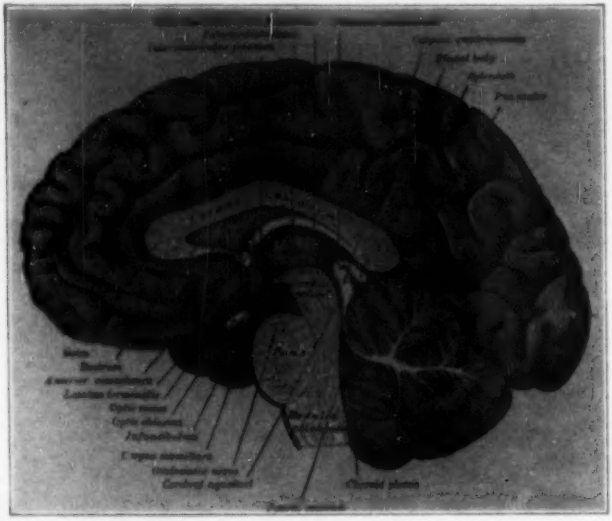

Fig. 9.—Sagittal section of the brain, showing the relation of the chiasm to the anterior wall of the third ventricle. (From Gray, H.: Anatomy of Human Body, ed. 23, edited by Charles Mayo Goss, Philadelphia, Lea & Febiger, 1948, p. 835, fig. 717.)

nerve. In 4 cases the globes were unavailable for examination. In 1 case the nerve was invaded from the orbit. In 7 of the aforementioned 10 cases generalized leptomeningeal involvement was present. In 2 other instances the process remained confined to the pia-arachnoid of the optic nerves and chiasm. In a third case the intracranial portion of the optic nerve represented the only intracranial extension of the tumor. In 9 of the 10 cases in which the optic nerve was observed to be involved at autopsy the optic chiasm was invaded.

In 7 of these 9 cases with generalized leptomeningeal involvement the route of dissemination was from the affected optic nerve and chiasm.

The eighth case is unusual and interesting. The tumor had extended from the right orbit to the right maxillary sinus and the right nasal cavity. From the latter it perforated through the right cribriform plate to invade the dura, the leptomeninges, from whence it spread diffusely, and the right frontal lobe. The chiasm was not involved in this patient. In the ninth case localized meningeal invasion had occurred by direct spread from neoplastic areas in the calvaria. Thus it may be said that in most instances leptomeningeal invasion is a direct spread from the involved optic nerve.

Once the chiasm has become involved, invasion of the ventricles frequently follows, and it occurred in 7 cases. The anterior wall of the

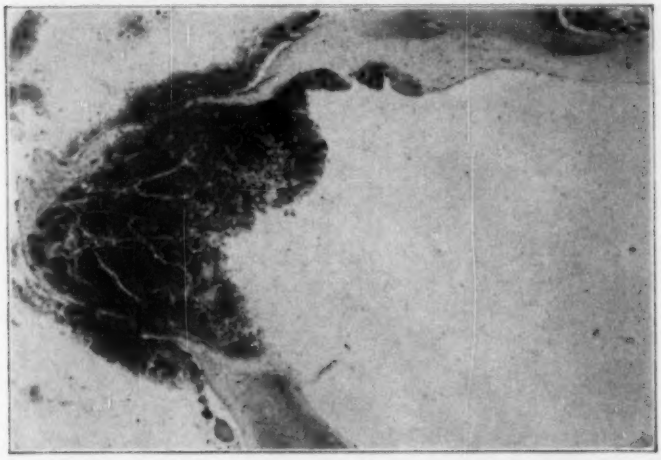

Fig. 10.—Section of the anterior wall of the third ventricle. Retinoblastoma is shown extending into the ventricle from the chiasm. The cavity of the ventricle is to the right and is distended. The area outlined is shown enlarged in figure 11.

third ventricle is formed above, in the region of the optic recess, by the thin lamina terminalis. Just below this is the optic chiasm itself, which projects into the cavity. Posteriorly and below the chiasm is the thin wall of the tuber cinereum (fig. 9). Thus, once the subarachnoid space is infiltrated, the tumor can easily penetrate directly into the third ventricle—usually through the thinner portions of its anterior wall—the lamina terminalis or the tuber cinereum. This method of ventricular invasion was shown microscopically in 5 cases (figs. 10 and 11). In the sixth case, with widespread involvement of the subarachnoid space of the brain and cord, the tumor had entered the tela choroidea of the ventricles and some of the papillae of the choroid plexus. Implants of

tumor in the wall of the ventricles probably occurred by way of the subarachnoid space, owing to retrograde passage of tumor cells from that space. In the seventh case, with ventricular involvement, the route of dissemination was not apparent. In all these 7 cases there was internal hydrocephalus of varying degrees.

Spinal Cord.—In 3 cases, or 17.6 per cent, the subarachnoid space of the spinal cord was involved in the spread of the tumor, and in 2 of these cases there was actual superficial invasion of the cord itself (fig. 12). In 2 cases the peripheral nerve roots and the cauda equina were

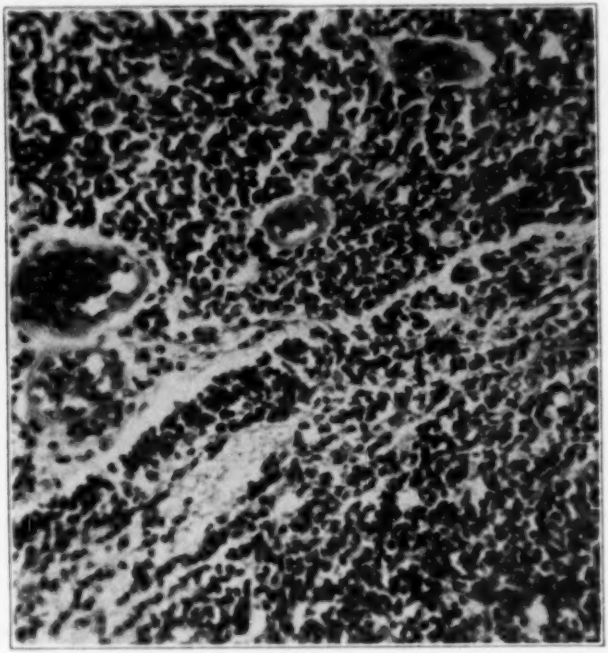

Fig. 11.—Enlargement of the area outlined in figure 10, showing retinoblastoma invading the anterior wall of the third ventricle.

invaded (fig. 13). In all these cases there was widespread dissemination of the tumor throughout the cerebral subarachnoid space, and it is easy to understand how the continued spread in this space, aided by the circulating spinal fluid, could produce involvement of the entire cord. The dura was never invaded. In a fourth case localized epidural masses were present in the cervical and lumbar portions of the cord. The

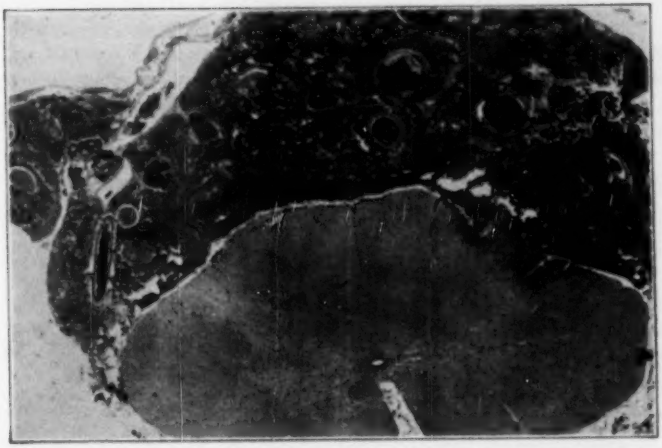

Fig. 12.—Section of the thoracic region of the spinal cord, showing retinoblastoma cells in the subarachnoid space and superficial invasion of the cord itself.

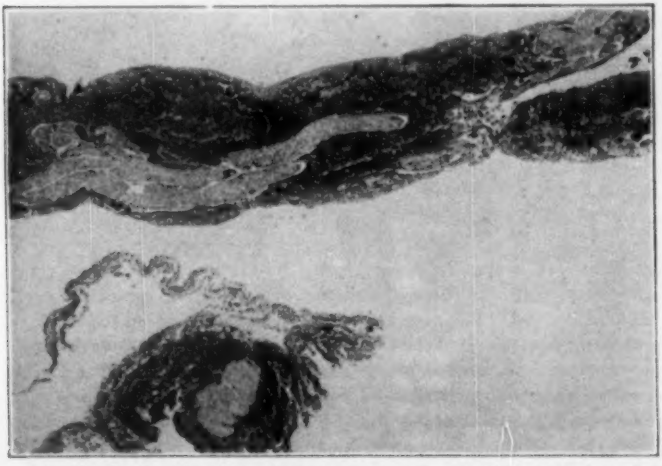

Fig. 13.—Section of cauda equina and a nerve root, showing invasion by retinoblastoma.

epidural fat was invaded, and there was early infiltration of the underlying dura. The method of spread in this case is not apparent. The cerebral meningeal involvement was localized to areas contiguous with metastatic lesions in the calvaria. Since there were extensive metastases to distant bones and viscera, this spinal involvement may represent a blood-borne metastasis. The vertebrae were not grossly invaded. In the remaining 5 of the 9 cases showing leptomeningeal invasion the spinal cord was not examined at autopsy. If this metastatic possibility is looked for in subsequent examinations, it will undoubtedly be found more frequently. The subarachnoid spread of the tumor to involve the cord was described in 1869 by Knapp,[23] and since then at least 5 additional cases of a similar nature have been reported.

In 2 of the cases in this series, tumor cells were observed in the cerebrospinal fluid before death, thus establishing this locus of spread clinically. As far as is known, these cases are the first in which this metastasis has been demonstrated clinically.

Distant Metastases.—It is interesting and important to realize the frequency of distant metastases in these cases, for 9 of the 17 cases, or 52.9 per cent, gave evidence of the disease at sites other than local or intracranial. In table 3 it is seen that the metastases were located in the bones in 9 cases (52.9 per cent), in the viscera in 8 cases (47 per cent) and in the lymph nodes in 8 cases (47 per cent).

Distant Bones.—It is difficult to evaluate properly the relative frequency with which any given bone is likely to be invaded because few routine autopsies include a thorough examination of these structures, unless there is an obvious mass. The ribs showed the highest incidence of metastases in this series, but this may be more apparent than real. In most autopsies the thorax is opened and these metastatic areas are at once visible. Knapp,[24] in 1924, in discussing an autopsy in a case of retinoblastoma, stated that this disease seemed to have a predilection for young, growing bone, and this observation is amply verified in this series. This occurrence may be explained by the fact that these metastases are medullary, being blood borne, and that in children the hemopoietic system is strongly functioning, giving the tumor emboli a rich, nutrient bed. The high incidence of bilaterality would tend to lend confirmation to this explanation. The vertebrae must also be infected via the blood stream, since there is no evidence to show direct spread from the subarachnoid space of the cord. The situation here with regard to the dura is the same as that found intracranially. The bones involved

23. Knapp, H.: Treatise on Intraocular Tumors, from Original Clinical Observations and Anatomical Investigations, New York, William Wood & Company, 1869.

24. Knapp, A.: Autopsy Report of a Case of Bilateral Glioma Retinae with Gliomatous Involvement of the Iris, Arch. Ophth. **53**:470-475 (Sept.) 1924.

are listed in table 3 and indicate the extensiveness of the osseous dissemination (fig. 14). In the few instances in which serum phosphatase studies were made the results were normal.

The metastases to distant bone are obviously blood borne, but with regard to the mode of spread to the bones of the skull there is more discussion. Metastatic areas in the calvaria were present in 9 cases, or in 52.9 per cent. Direct spread from the affected orbit may occur and

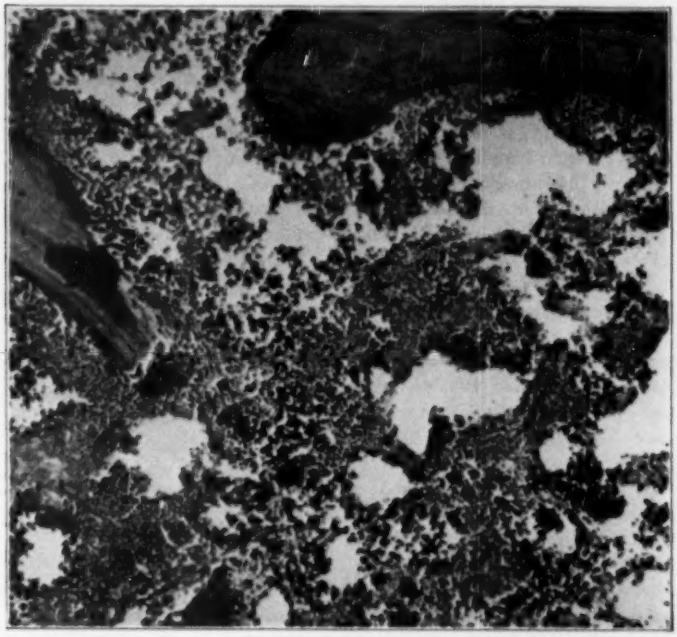

Fig. 14.—Section of the humerus, showing metastatic retinoblastoma in the medullary cavity.

was seen in 4 cases in this series. In 2 cases the disease spread through the nasal wall of the affected orbit to the nose and thence through the cribriform plate. In the other 2 cases the frontal, sphenoid and temporal bones were involved by direct spread from the orbit. In all these 4 cases there were extensive metastatic areas throughout the calvaria. Knapp [23] (1869) described direct invasion of the left temporal bone from the left orbit. Meighan and Michaelson [25] (1938) stated that orbital

25. Meighan, S., and Michaelson, I. C.: A Case of Glioma Retinae with Special References to the Mode of Spread, Tr. Ophth. Soc. U. Kingdom **58**:208, 1938.

invasion is a necessary preliminary to involvement of the skull. They expressed the belief that the spread was probably via the lymphatics. This is difficult to understand, since, as Duke-Elder [26] stated:

> In the orbit there are no lymphatic nodes, and no lymphatic vessels have been demonstrated. Furthermore, such lymph drainage as exists from the orbit accompanies the veins through the inferior orbital fissure to the internal maxillary nodes and thence to the superior deep cervical nodes.

In our series, in only 5 of the 9 cases with metastases to the bones of the skull was there orbital invasion. On the contrary, orbital invasion was present in 11 cases, only 5 of which showed disease in the calvaria. The conclusion seems justified that orbital disease, if present for a sufficient length of time, may spread to involve the adjacent bones of the skull. This is probably a direct dissemination, rather than spread along possible lymphatics. Time is undoubtedly the important factor. However, the metastatic areas in the calvaria not adjacent to the orbit are multiple, and, although they may be confluent, they are frequently isolated tumor masses. Therefore, another method of spread seems likely.

In an attempt to determine the manner by which the bones of the skull are invaded, the cases showing such invasion were compared with those with metastases to distant bones. An interesting correlation exists. In all but 1 case with invasion of the calvaria there were distant osseous metastases as well, and in this instance examination of the peripheral bones was not made. On the other hand, in only 1 of the cases with metastases to distant bones was the calvaria not invaded. Furthermore, in 8 of the 9 cases with distant osseous metastases there was visceral involvement as well, so that a correlation similar to that of metastases to distant bones exists with regard to invasion of the bones of the skull.

Invasion of blood vessels must and does occur. Leber [27] (1916) reported 2 cases of invasion of the venae vorticosae but agreed that the most logical and most frequent site of vascular invasion is the choroid. Wintersteiner [2] and Nattini [28] (1910) proved that cells grow into the thin-walled choroidal vessels. In the pathology collection of the Institute of Ophthalmology is a specimen showing, on serial sections, invasion of the central retinal vein (figs. 15 and 16). In the literature examined this possibility was not mentioned.

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26. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1946, vol. 1, p. 188.

27. Leber, T.: Die Geschwulstbildungen der Netzhaut: Das Gliom oder der Markschwamm der Netzhaut, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, W. Englemann, 1916, vol. 7, pp. 1723-1863.

28. Nattini, cited by Leber.[27]

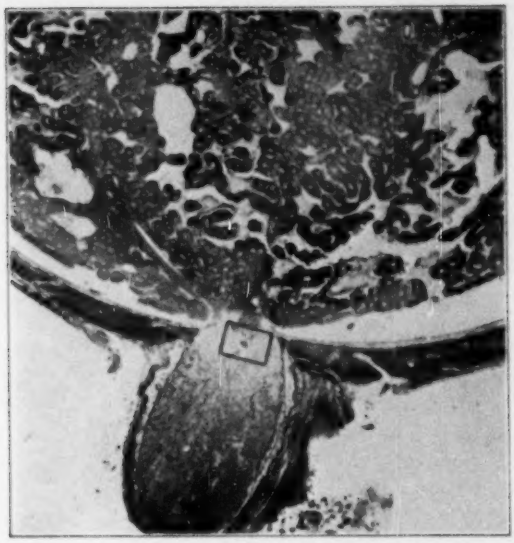

Fig. 15.—Invasion of the nerve and central retinal vein. Low power section of posterior portion of globe from which figure 16 is taken (see area outlined).

Fig. 16.—Tumor in the central retinal vein. High power view of the area indicated in figure 15, showing retinoblastoma cells within the central retinal vein.

Since the metastases to the peripheral osseous areas are unquestionably blood borne, the relation of choroidal to skeletal invasion was studied. Unfortunately, since the globes in 4 cases of distant osseous metastases were unavailable for examination, the enucleation having been performed elsewhere, the information is incomplete. However, in every instance of invasion of the skull bones, distant bones or viscera in which the globe was examined the choroid was involved. Three of the 8 cases of choroidal invasion failed to show evidence of visceral metastases, but the bones were not examined.

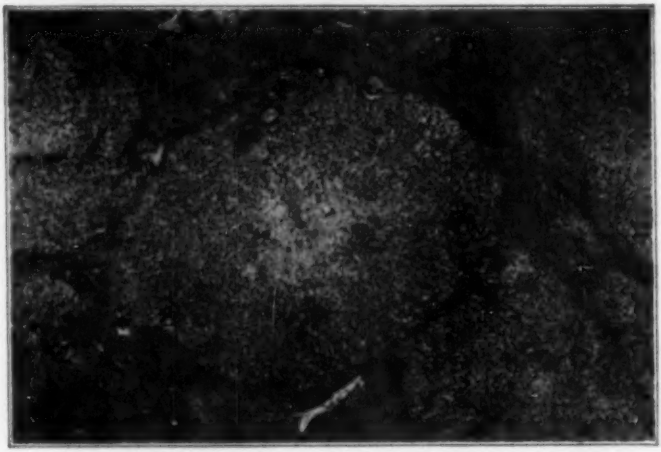

Fig. 17.—Section of liver showing nodular areas of metastatic retinoblastoma.

Involvement of the calvaria, as observed in this series, seems to be produced in one or both of two ways, by direct spread from the affected orbit or by blood-borne metastases.

Viscera.—Invasion of various viscera was observed in 8 cases, or 47 per cent, an incidence considerably higher than that usually found in the literature. In fact, cases of retinoblastoma in which the patient dies with visceral metastases are usually reported as rarities. The visceral involvement is comparable to the incidence of metastases to distant bones, i. e., 52.9 per cent. In this series the liver was involved in 5 instances, or 29.4 per cent, and was the organ oftenest affected (figs. 17 and 18). The other organs invaded, in the order of their frequency, were as follows: kidney, 2 cases (1 bilaterally); testis, 2 cases (1 bilaterally) (fig. 19); pancreas, 1 case; spleen, 1 case; ovaries, 1 case (bilaterally)

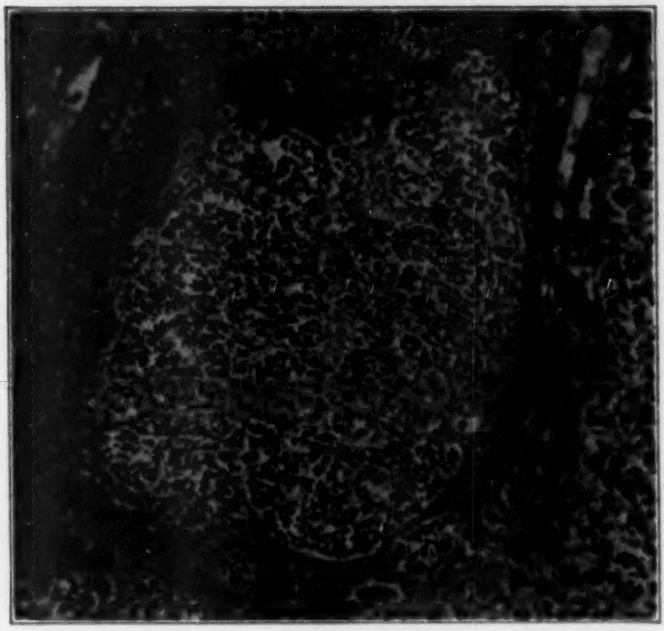

Fig. 18.—Higher magnification of figure 17 showing a focus of retinoblastoma metastasis in the liver.

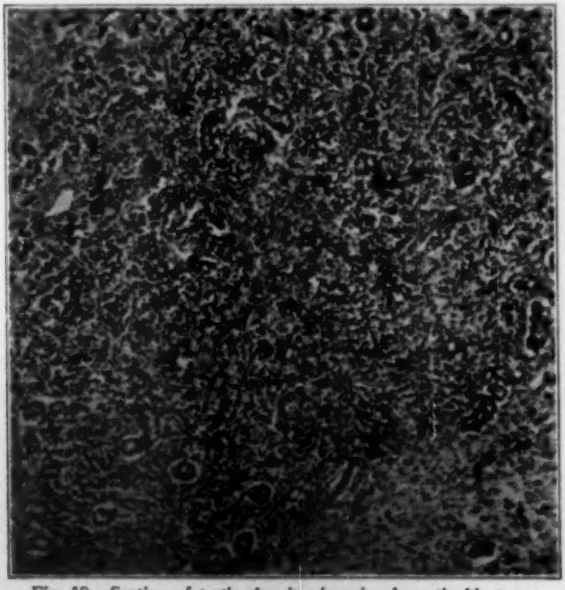

Fig. 19.—Section of testis showing invasion by retinoblastoma.

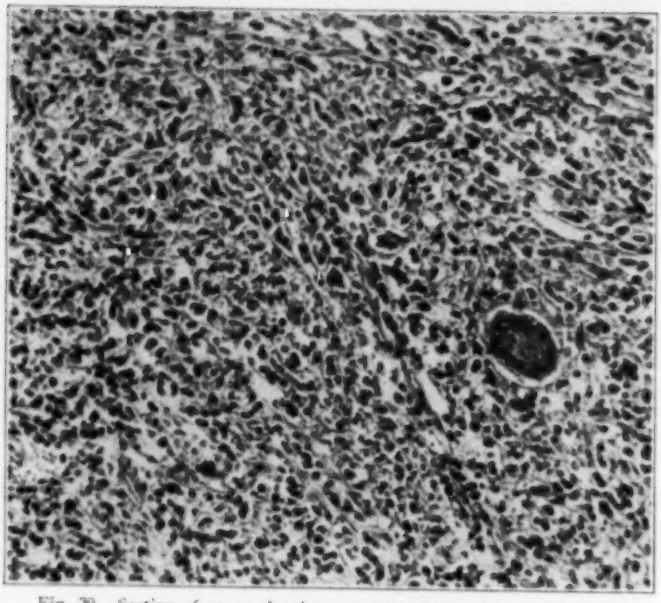

Fig. 20.—Section of ovary showing metastatic focus of retinoblastoma.

Fig. 21.—Section of the wall of the uterus showing invasion by retinoblastoma.

(fig. 20), and uterus, 1 case (fig. 21). Metastases to these organs are obviously blood borne. In 1 case the wall of the abdominal aorta was superficially invaded (fig. 22), by direct extension from adjacent metastatic areas.

The invasion of the liver is nodular and is never sufficient to produce jaundice or signs of hepatic insufficiency. In 2 cases this organ was enlarged. The metastatic areas in the other viscera were not diagnosed clinically, except in 1 case. In this instance an abdominal mass was felt while the patient was receiving radiotherapy to the remaining eye.

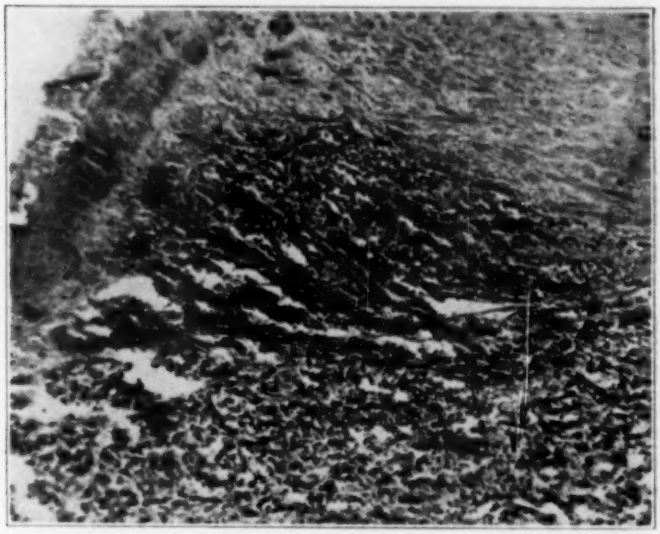

Fig. 22.—Section of the wall of the abdominal aorta showing invasion of the adventitia by retinoblastoma. This was a direct extension from adjacent metastatic foci.

At operation, massive metastatic involvement of the right ovary was found and confirmed microscopically.

These visceral metastases are blood borne. In most instances the invasion of the blood vessels appears to take place in the choroid, as has been stated. The important consideration is the frequency of their occurrence.

Lymph Nodes.—Involvement of the various lymph nodes throughout the body was noted in 8 cases, or 47 per cent. In most cases at autopsy only the grossly involved nodes were taken for sectioning, so that one

may have a somewhat limited picture of the widespread involvement of the lymphatic system possible in this disease. One might better say that obvious invasion of the lymph nodes was present in 47 per cent, for consideration of table 4 leaves one with the feeling that other nodes must certainly have been diseased, at least microscopically, since the nodes draining many of the involved areas were not mentioned (fig. 23).

The spread to the cervical nodes obviously results from the local disease. In every case with this type of involvement local invasion was

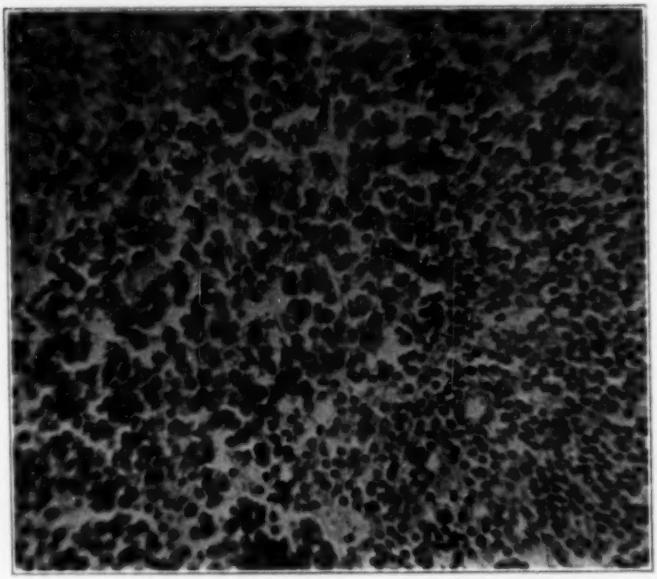

Fig. 23.—Section of a lymph node showing involvement by retinoblastoma.

proved to exist, and by "local" is meant either a recurrence in the orbit or an invasion of the adjacent bones, sinuses, nose or mouth. In 2 instances, however, there was local disease without involvement of the regional nodes. Neither the parotid gland nor the preauricular nodes were involved. In the literature, the parotid gland is not commonly said to be invaded, and its invasion usually results from bulky, local disease spilling out of the orbit and directly invading the gland.

That the other areas of involvement of lymph nodes are due to lymphatic drainage from regional metastases is apparent from table 4.

TABLE 4.—*Relation of Invasion of the Lymph Nodes to Metastases*

Case No.	Nodes	Other Metastases
5	Cervical, retroperitoneal, mesenteric	Skull bones, tibia, fibula, paravertebral muscles in abdomen
6	Cervical, inguinal, femoral	Orbital recurrence, skull bones, clavicle, ribs, radius, femur, fibula, pancreas
7	Hilar	Skull bones, ribs, sternum, thoracic vertebrae, lumbar vertebrae, ilium, ischium, pubis, liver
8	Pancreatic	Skull bones, ribs, sternum, thoracic vertebrae, lumbar vertebrae, ilium, liver, kidney
9	Cervical, hilar, tracheobronchial, axillary, epitrochlear, retroperitoneal, inguinal, popliteal, iliac	Orbital recurrence; meninges; clavicle; ribs; humeri; ulnas; radiuses; cervical, thoracic and lumbar vertebrae; sacrum; ilia; ischia; pubes; femora; tibias; fibulas; scapulas; testes
10	Cervical, retroperitoneal	Orbital recurrence, meninges, cerebral cortex, cribriform plate, sphenoid, nose, maxillary sinus, ethmoid sinus, ribs, liver
16	Cervical	Calvaria, frontal bone, zygoma, maxilla, sphenoid, mandible (bilateral), sternum, liver, testes, clavicle, ribs, humerus, ulna, radius, tibia, fibula, femur
17	Hilar, infraclavicular, axillary, retroperitoneal, inguinal, perivesicular	Calvaria, cerebral dura, epidural space of spinal cord, femur, radius, ulna, ribs, iliac crest, uterus, ovaries, liver

Local Invasion.—Once outside the globe, the tumor may grow locally in the orbit and invade the surrounding bones, penetrating into the sinuses, the mouth and the nose, and from the nose it may perforate the cribriform plate to enter the cranial cavity. Local invasion, as defined here, was found in 7 cases, or 41.2 per cent. The orbit may be involved in several ways, e. g., from the tumor perforating the sclera along an emissary, from the optic nerve, by direct scleral perforation or by rupture of the globe. It is interesting that in 2 cases the disease spread from one orbit to the other through the nose. Table 3 lists the areas of local invasion.

GENERAL CLASSIFICATION

In this classification each case was listed according to the location of its metastases.

Intracranial cavity only (cases 2, 12 and 14)	3	8 (47 per cent)
Intracranial cavity and spinal cord (cases 11, 13 and 15)	3	
Intracranial cavity and local structures (case 1)	1	
Intracranial cavity, skull and local structures (case 6)	1	
Skull and distant organs (case 7)	1	9 (53 per cent)
Skull, distant and local structures (cases 5 and 16)	2	
Intracranial cavity, skull bones and distant structures, (cases 8 and 3)	2	
Intracranial cavity, local and distant structures (case 9)	1	
Intracranial cavity, skull, local and distant structures (cases 4, 10, 17)	3	

It is apparent from this grouping that 8 patients (47 per cent) died with the disease confined to the head and/or the spinal cord. The other

TABLE 5.—*Sites of Metastasis*

Case No.	Author, Date	Sex	Age	Eye Involved	Choroid	Optic Nerve	Optic Chiasm	Brain and Ventricles
1	Wilson and Thomson,* 1900	M	4 yr.	O. D.	+	+ (O. D.); nerve invaded at globe; subarachnoid and subdural space; sheath of left nerve distended	Normal; mass comes in from right orbit; chiasm enclosed in "a clot of blood"	Base and sides studded with nodules; much thin fluid at base; necrosis of right frontal lobe without invasion; nodules on right cortex over midlobe—and on left—without invasion; subarachnoid space around nodules infiltrated
2	Fehr, Centralbl. f. prakt. Augenh. **24**:129-136, 1900	M	1½ yr.	O. S.	--	O. S.: + O. D.: —	Involved	.....
3	Owen,** 1906	?	?	O. U.	?	?	+	—
4	Parsons, J. H.: Roy. London Ophth. Hosp. Rep. **18**:141-149, 1904-1906	F	1½ yr.	O. U.	—	--	+	..
5	Radcliffe, M., and Goldberg, H. G.: Arch. Ophth. **36**:223-232, 1907	F	2 yr.	O. S.; O. D. at autopsy	+	O. S.: +; nerve filled; no normal nerve bundles seen; many blood spaces; subarachnoid space invaded; dura perforated O. D. (at autopsy): subdural and subarachnoid spaces	--	+
6	Gardiner, J. P.: Arch. Ophth. **37**:667-671, 1908	?	3¼ yr.	O. U.	— O. S.	O. D.: +	--	..
7	Reeder, D. F.: Ophth. Rec. **25**:79-80, 1916	M (Negro)	2 yr.	O. U.	..	O. U.: +	..	Left frontal lobe compressed, as well as cerebellum and occipital area
8	Taylor, F. E., and Fleming, N. B. B.: Brit. J. Ophth. **1**:92-99, 1917	F	3 yr.	O. U.	+ O. U.	O. D. + (at operation); O. S.: +	+	..
9	Kusama, K.: Am. J. Ophth. **2**:636-650, 1919	?	5 mo.	O. U.	—	?	?	Dura
10	Knapp,** 1924	F	2 yr.	O. U.	+	O. D.: Sheath full O. S.: +	+	Right middle fossa; thalamus
11	Parker, W. R., and Stokes, W. H.: J. A. M. A. **87**:1901-1907 (Dec. 4) 1926	M	5 yr.	O. S.	?	..	..	+ Meninges; dura
12		M	21 mo.	O. U.	+	O. D.: Sheath infiltrated and nerve	..	+ Cranial cavity

in Reported Cases with Autopsy

Bones of Skull	Spinal Cord	Orbital Bones	Facial Bones	Lymph Nodes	Viscera	Distant Bones	Comment
..	..	..	..	..	..	..	Autopsy incomplete; rest of body not examined
Left frontal area and on convexity; tumor growing inward and 3 perforations of dura	..	Maxilla, left and right side	..	Mediastinal	Pleura of left lung; liver	Ribs; sternum	..
Invaded, with scalp	..	..	..	..	..	..	..
Cranial bones and scalp	..	Roofs of orbit raised so inferior surfaces of frontal lobes pitted but not infiltrated	..	..	..	..	Head only examined
..	Sheath filled and cord invaded	..	..	..	Liver	..	..
Skull covered; lying under periosteum; parietal, frontal and occipital areas show masses on interior surface; tumor bulging from sutures; tumors on outer aspect connected with those on inner; cribriform plate invaded	Canal and dura infiltrated; peripheral nerves normal	Maxilla; ethmoid; lacrimal	Turbinate and nasal bones	Recurrence in right orbit continuous with cervical nodes; tracheobronchial, supraclavicular and infraclavicular involved	Pleura, bilateral; testis, bilateral	Ribs; periosteum of vertebrae; ilia; coccyx; pubes; ischia; tibia, right; fibula, right; femur; sternum	..
Masses over all bones; penetration and attachment to dura	..	..	..	Submaxillary; cervical; inguinal; pelvic	Parotid gland; liver	..	..
Twenty areas of invasion	..	..	..	Mesenteric	Ovary, right	Second lumbar vertebra	..
+; tumors within cranium and dura; right parietal area and others	..	..	..	..	Liver; pancreas	..	..
Inner surface invaded subperiosteally; some externally; dura invaded; inner and outer masses not joined	..	Maxilla, left; frontal, right	..	..	Liver	Ribs; ilium, left	..
..	..	..	..	..	Liver	..	..
+	..	Zygoma, right	..	Cervical, right	..	..	..

Case No.	Author, Date	Sex	Age	Eye Involved	Choroid	Optic Nerve	Optic Chiasm	Brain and Ventricles
13	Nitsch, M.: Abhandl. a. d. Augenh. u. Ihr. grenzgeb. **5**: 1-106, 1927	F	1½ yr.	O. S.	..	O. S.: +; nerve and sheath involved; tumor lying outside, too; in midorbit only sheaths involved; extension from chiasm to right nerve; O. D.: Tumor extending to lamina cribrosa; tumor lying in subdural and subarachnoid spaces	+	Internal hydrocephalus; meninges
14		M	2 yr.	O. S.	..	O. S.: +; nerve and sheaths O. D.: subarachnoid space not involved; extension from O. S.	+	Ventricles enlarged; meninges
15	Benedict, W. L.: Arch. Ophth. **2**: 845-848 (Nov.) 1929	F	4 yr.	O. S.	..	O. S.: + near globe; — at cut end	..	Brain; internal hydrocephalus
16	Hu, C. H.: Am. J. Path. **6**: 27-37, 1930	M	4 yr.	O. S.	..	O. S.: +	..	+ Dura; ? left frontal lobe
17		M	3 yr.	O. S.	+ Ciliary body	O. S.: + at globe O. D.: Intraorbital from chiasm	+	Brain, choroid plexus, meninges; tumor covering surface of brain via subarachnoid space, and even over the cerebellum, pons and medulla; superficial invasion of cerebrum and cerebellum; lateral ventricle slightly dilated
18	Cairns, H., and Russell, D. S.: Brain **54**: 377-420, 1931	M	3 yr.	O. S.	+	O. S.: + O. D.: +; near chiasm and in nerve and sheath; tumor cells along ophthalmic artery in nerve; some cells in disk; tumor cells in sheaths and extended into choroid	+	Meninges, third ventricle, tela choroidea, fourth and lateral ventricles, choroid plexus (right); moderate internal hydrocephalus; cortex and cerebellum invaded
19	Jaffe,* 1934	F	2 yr.	O. D.	..			
20	Rand, C. W.: Arch. Ophth. **11**: 997-994 (June) 1934	F	4 yr. 7 mo.	O. S.	..	O. S.: Nerve invaded at cut end; proximal end of nerve and sheath, obtained at operation, involved. O. D.: Tumor in subarachnoid space and nerve; tumor emboli seen in vessels	+	Subarachnoid space; superficial cortical invasion on inferior surface of cerebellum
21	Lederer, J., and Moreaux, J.: Rev. belge sc. med. **10**: 79-86, 1938	M	6 yr.	O. D.	..	..	..	..
22	Meighan and Michaelson,[23] 1939	M	3½ yr.	O. U.	..	O. S.: Tumor present just behind globe; then free up to 0.80 mm., when tumor cells reappeared; in center first with gradual spread to subarachnoid space	—	Dura
23	Ch'in, K. Y.: Am. J. Path. **17**: 813-819, 1941	F	21 mo.	O. U.	O. D. + O. S. —	..	..	Pressure atrophy only
24	McCrea, W. R. F.: Tr. Ophth. Soc. **15**: 416-418, 1945	F	2 yr.	O. D.	+	..	+	Mass in third ventricle

Cases with Autopsy—Continued

Bones of Skull	Spinal Cord	Orbital Bones	Facial Bones	Lymph Nodes	Viscera	Distant Bones	Comment
..	Down to cauda equina	..	..	..	..	..	..
..	..	..	..	..	..	..	..
..	..	..	..	..	..	..	..
Frontal, left; parietal, left	Meninges and outside dura, sacral region	..	..	Retroperitoneal; inguinal; cervical	Pleura; parotid gland	..	Eyelids invaded
..	+ pia arachnoid, cord and cauda equina	..	..	..	..	..	..
..	Subarachnoid space full; cord invaded at second thoracic and first lumbar vertebra; nerve roots invaded	..	..	..	..	..	All cranial nerves embedded in tumor
Temporoparietal, left	..	Zygoma; orbital bones, right	Mandible, right side (near articulation)	Cervical	Liver; ovary, left	..	Left eye normal; scalp invaded
..	..	..	..	..	..	..	..
Bones studded	..	..	..	..	..	Fourth and twelfth dorsal vertebrae; left tibia	..
Numerous tumors in cranial bones	..	Roof of orbit, right	..	Cervical, right; mediastinal	Liver	..	..
Temporal, right; parietal, right; occipital, right; temporal, left; petrosal, left; parietal, left	..	Frontal, right; sphenoid, right; ethmoid, right	Maxilla, bilaterally; hard palate; mandible, bilaterally; ethmoid sinus	..	Liver; pancreas	Ribs, bilaterally; femurs; tibias; fibulas; humeri	Muscle of right thigh invaded
..	..	..	..	..	..	..	..

9 patients (53 per cent) had distant metastases in addition to those present within the skull. Retinoblastoma is usually considered to extend only locally or intracranially. That it does involve these areas is evident, for all the patients had the disease either in the calvaria or intracranially. However, the high incidence of distant, blood-borne metastases is not generally recognized.

ESTIMATED CAUSE OF DEATH

It is often extremely difficult to determine the exact cause of death at autopsy, and in cases of retinoblastoma this is rendered even more difficult when one tries to decide whether death was due primarily to the intracranial or to distant metastases or to both. After each case was analyzed as to the location of the metastases and the extent of the disease present in each area, as determined from the autopsy report and the microscopic sections, and these data were compared with the clinical course, the causes of death were estimated as follows:

Intracranial (internal hydrocephalus, 7 cases) 9 (52.9%)
(Cases 1, 2, 3, 10, 11, 12, 13, 14, 15)
Generalized carcinomatosis 7 (41.2%)
(Cases 4, 5, 7, 8, 9, 16, 17)
Local disease 1 (5.9%)
(Case 6; massive invasion of the nose and mouth, making respiration and deglutition impossible)

ANALYSIS OF REPORTED CASES WITH AUTOPSY

In order to evaluate further the cases presented here, 24 autopsies reported in the literature since 1900 were analyzed with regard to sex, average age, eye involved and sites of metastasis. It is not possible to estimate the cause of death in these cases. There were 11 males, and 10 females, and for 3 the sex was not specified. The average age was 2 years 11 months. The right eye was involved in 4 cases; the left, in 9 cases, and in 11 cases the involvement was bilateral. The sites of metastases are shown in table 5.

Arrangement of these cases according to the metastatic areas, as was done in the 17 cases being presented, resulted in the following classification:

Intracranial cavity only	5	
Intracranial cavity and spinal cord	3	
Intracranial cavity and skull	1	11 (45.8%)
Intracranial cavity, skull and local structures	1	
Skull and local structures	1	
Intracranial cavity and distant organs	1	
Intracranial cavity, spinal cord and distant structures	1	
Skull and distant structures	1	13 (54.2%)
Skull, local and distant structures	2	
Intracranial cavity, skull, local and distant structures	8	

A comparison of the classifications of the two series is interesting and enlightening. The most salient fact is the agreement between the two with regard to the frequency of distant metastases. In the present series 47 per cent of patients were found to have died with the disease confined to the head and central nervous system, and for the collected series the figure is 45.8 per cent. A larger proportion, 53.0 and 54.2 per cent respectively, died with distant metastases. The distant bones were found to be involved in this series in 52.9 per cent of the cases, as against 25.0 per cent in the reported cases. This may be explained by the completeness of the autopsies. The present series showed 29.4 per cent with metastases to the liver, as against 37.5 per cent in the series from the literature. These figures, and those for invasion of the skull, lymph nodes and spinal cord are presented in the following tabulation:

	Present Series (17 Cases)		Collected Series (24 Cases)	
Metastasis	No.	%	No.	%
Bones of skull	9	52.9	14	58.3
Distant bones	9	52.9	6	25.0
Spinal cord	4	23.5	6	25.0
Lymph nodes	8	47.0	8	33.3
Viscera	8	47.0	12	50.0

SUMMARY

Autopsies in 17 cases of retinoblastoma are analyzed. The sites of metastatic spread and their relative frequency are tabulated, and the method of dissemination to these areas is discussed. It was found that although 16 of the cases, or 94.1 per cent, had some form of intracranial metastasis, only 8, or 47 per cent, died with the disease confined to the head and/or spinal cord. In the other 9 cases, or 53 per cent, there were distant metastases in addition to those present within the skull. The lymph nodes were involved in 8 cases, the skull bones in 9, distant bones in 9 and viscera in 8 cases. The cases are classified according to the areas involved, and this classification is compared with a similar one prepared from cases reported in the literature. The most important aspect of this analysis is the finding that retinoblastoma is by no means the purely local and cranial disease it is so often considered. It is, rather, a highly malignant, widely disseminated neoplasm. On this subject, Jackson [29] (1929) stated:

In the great majority of fatal cases, metastasis occurs. This fact has been concealed because glioma of the brain and glioma of the retina were regarded as the same disease. In the former, there are no metastases—in the latter, many. To writers more familiar with the former, the conclusion seemed justified that metas-

29. Jackson, E.: Retinoblastoma and Recent Views of Malignancy, J. A. M. A. **87**:1471-1477 (Oct. 30) 1926.

tases were rare or unusual; and this view is encountered in works on general pathology and in papers of ophthalmologists who have taken this view from the literature, even when reporting as unusual cases of retinoblastoma with metastases. Of all the fatal cases comparatively few are subjected to necropsy, and of these still fewer are thoroughly searched for the evidence of all such extensions.

ABSTRACT OF CASES

Case 1.—E. T. was first seen in Vanderbilt Clinic, Presbyterian Hospital, New York, on April 5, 1929, with a history that one year before his admission the mother had noticed a white reflex in the pupillary area of the right eye. This gradually enlarged, and vision became increasingly worse. Examination revealed increased intraocular tension, a dilated fixed pupil and a yellowish white mass in the fundus, which extended forward into the vitreous. The left eye was normal. Enucleation of the right eye was done at Presbyterian Hospital on June 4. After operation, he was given radium treatments elsewhere. On November 2, there was a recurrence in the right orbit and signs of intracranial extension appeared. He died on Dec. 3, 1929.

The anatomic diagnosis at autopsy was (*a*) glioma of the retina, right eye, with extension into the optic nerve; (*b*) glioma of the cerebrum, and (*c*) recurrent glioma involving the right orbit, the sphenoid and ethmoid bones, the vomer and the right side of the superior maxilla.

Case 2.—A. B. was first seen in February 1934, with a history of cloudiness of the left eye and stumbling gait. The left eye was enucleated at the Knapp Memorial Hospital, New York, in July 1934. Postoperative roentgen and radium therapy was given at the Memorial Hospital for the Treatment of Cancer, New York, for recurrent disease in the left orbit, which appeared two weeks after operation. The patient died Dec. 27, 1934.

The anatomic diagnosis at autopsy was (*a*) recurrent retinoblastoma; (*b*) retinoblastoma, metastatic to the brain and periosteum; (*c*) internal hydrocephalus; (*d*) subperiosteal metastases to the calvaria, and (*e*) infection of the left orbit.

Case 3.—V. G. was first seen at Memorial Hospital on Feb. 28, 1936, with a history that in June 1935 a yellowish reflex was noted in the right pupil, with subsequent impairment of vision. In November 1935 the right eye was enucleated. When the patient was first seen, there were multiple metastases throughout the body. These were treated with roentgen radiation. The patient died on May 13, 1936.

The anatomic diagnosis at autopsy was retinocytoma with metastases to the cervical and retroperitoneal lymph nodes and to multiple bones.

Case 4.—R. K. was first seen at the Memorial Hospital on July 16, 1935 with a history that ten months before the left eye had become irritable and there was considerable discharge. Shortly thereafter the eye became more prominent. Four weeks previously the left eye had been enucleated, and the patient was referred for prophylactic roentgen therapy. At the examination, a mass was palpable in the left orbit, but this appeared to regress under treatment. On March 23, 1936 enlarged axillary nodes were found, and there was roentgenologic evidence of destruction of bone in the left ilium. On April 23, a nodule was palpable in the left frontal region. Other metastases appeared in the region of the ninth dorsal vertebra, in the skull, the left maxillary region and zygoma, in the right humerus and in both arms and hands. These lesions were treated with roentgen radiation. The patient died June 21, 1936.

Anatomic diagnosis at autopsy was recurrent glioma of the retina (primary in the left eye) with metastases to the brain, skull, right kidney and ninth thoracic vertebra.

Case 5.—J. P. was first seen at Memorial Hospital, New York, on Feb. 6, 1936, with a history that at the age of 9 months the left eye appeared larger than the right. At the age of 11 months there was a white reflex in the right pupil. In July 1935 the left eye was enucleated. In November 1935 recurrence was noted in the left orbit. Examination revealed a large mass in the left orbit, which was adherent to the lids. Roentgen and radium therapy were given. On May 28, 1936 an occipital mass was noted. On June 26, a mass appeared on the left side of the mandible. Subsequently, other metastases appeared in the head of the right fibula, the left shoulder and the left humerus. These were treated with roentgen radiation. The patient died on July 18, 1936.

The anatomic diagnosis at autopsy was (*a*) glioma of the left eye with postoperative recurrence in the left orbit, and (*b*) metastases to the skull, ribs, left humerus, right femur and fibula, clavicle, pancreas and inguinal and femoral nodes

Case 6.—R. O'R. was first seen at the Institute of Ophthalmology, Presbyterian Hospital, on Aug. 26, 1935, with a history of a head tilt to the left for three months. Examination with the child under anesthesia revealed bilateral retinoblastoma. Both eyes were irradiated, and the growth in the right eye showed satisfactory regression. On June 17, 1936 the left eye was enucleated. On Aug. 21, 1936 there were evidence of activity on the part of the tumor in the right eye and recurrent disease in the left orbit. The patient died on July 10, 1937.

The anatomic diagnosis at autopsy was (*a*) recurrent glioma with extension to (1) the nasal cavity and bones, (2) the right side of the maxilla and mandible and adjacent small bones, (3) the intracranial and nasal cavities and (4) the orbit opposite the nasal cavity involved; (*b*) metastases to the calvaria, and (*c*) increase in intracranial pressure.

Case 7.—R. W. was first seen on July 10, 1936, with a history that in February 1936 the parents noted a grayish reflex in the right pupil. Examination revealed retinoblastoma of the right eye, and roentgen therapy was given at the Memorial Hospital. On Dec. 9, 1936 the right eye was enucleated at the Institute of Ophthalmology. On March 16, 1937 a mass was noted in the left parietal region. On May 25 a metastasis was noted in the left femur, for which roentgen therapy was prescribed. The patient died on Sept. 13, 1937.

The anatomic diagnosis at autopsy was (*a*) glioma of the retina, right eye; (*b*) generalized subperiosteal metastases, and (*c*) metastases to the hilar nodes, the liver and the subcutaneous tissue of the thorax.

Case 8.—E. B. was first seen on Oct. 10, 1936 with a history that in January 1935 the mother first noted a whitish reflex in the right pupil. On Oct. 3, 1936 the right eye was enucleated, at the Manhattan Eye and Ear Hospital. On Jan. 19, 1937 recurrence was noted in the right orbit. The patient died on Oct. 4, 1937.

The anatomic diagnosis at autopsy was (*a*) glioma retinae, right eye, with retro-orbital extension; (*b*) disseminated subperiosteal metastases; (*c*) metastases to the liver; (*d*) metastases to the right kidney (?), and (*e*) increased intracranial pressure.

Case 9.—J. R. was admitted to Memorial Hospital on July 6, 1939, with a history that nine months previously a yellowish reflex was noted in the right pupil

and a diagnosis of bilateral retinoblastoma was made. On Dec. 11, 1939 the right orbit was exenterated, and on Feb. 7, 1940 the left eye was enucleated. The patient died on Feb. 25, 1940.

The anatomic diagnosis at autopsy was (*a*) recurrent bilateral retinocytoma with extension through the left optic foramen to the cranial cavity; (*b*) extensive generalized subperiosteal and medullary osseous metastases; (*c*) widespread metastases to the lymph nodes, and (*d*) metastases to both testes.

Case 10.—K. C. was admitted to the Institute of Ophthalmology on May 2, 1943, with a history that one year previously the right eye had become divergent. Recently, the parents had noticed a yellow reflex in the right pupil and prominence of the right eye with some redness and tenderness. A diagnosis of retinoblastoma of the right eye was made, and on May 4 the eye was enucleated. Examination of the left eye at this time showed a tumor obscuring the optic disk. Roentgen therapy was given to the left eye, with considerable regression in the size of the lesion. On Dec. 15, 1943 a recurrence was noted in the right orbit. On December 20 exenteration of the right orbit was done, and gold radon seeds were implanted in the optic nerve. Postoperative roentgen therapy was given. On March 23, 1944 a recurrence was present in the upper margin of the right orbit. Throughout the course of the illness the left eye showed no evidence of recurrent disease. The patient died on Nov. 13, 1944.

The anatomic diagnosis at autopsy was (*a*) residual retinocytoma of the right orbit with extension into the right maxillary sinus, and perforation of the right cribriform plate, with direct extension into the right frontal lobe; (*b*) metastatic retinocytoma in the right subdigastric node, the liver and the retroperitoneal lymph nodes, and (*c*) metastases to the spleen.

Case 11.—F. L. was admitted to the Institute of Ophthalmology on July 30, 1945 with a history that two months before a white reflex had been noted in the right pupil. One week before his admission the patient was struck on the right side of the head during a fall. On examination, the right anterior chamber was found to be filled with blood, and the fundus could not be visualized. He was discharged on August 7 and readmitted on Jan. 3, 1946 for reexamination. On January 16 the right eye was enucleated. On June 26 the patient was admitted to Babies Hospital, New York, with a history of vomiting and convulsions for two weeks. On July 10, examination of the spinal fluid revealed tumor cells (retinoblastoma). On July 16 the patient died.

The anatomic diagnosis at autopsy was (*a*) retinoblastoma, right eye; (*b*) extension of the retinoblastoma into the right optic nerve, leptomeninges and parenchyma of the brain and spinal cord, ventricles of the brain, cranial and spinal nerves and gasserian ganglions; (*c*) mild internal hydrocephalus; (*d*) acute ependymitis, and (*e*) dermoid cyst of the right frontal bone.

Case 12.—W. Y. was admitted to the Institute of Ophthalmology on Jan. 18, 1945, with a history that the right eye had turned in since birth. At the age of 1 year vision seemed to be poor in the right eye, and in December 1944 a yellowish reflex was noted in the right pupil. Examination revealed bilateral retinoblastoma. The patient was discharged, and the right eye was subsequently enucleated in the Episcopal Eye, Ear and Throat Hospital, Washington, D. C. The left eye was treated with roentgen radiation at the Memorial Hospital, New York. On Aug. 22, 1945 the lesion in the left eye showed renewed activity. The patient died at Children's Hospital, Philadelphia, on July 30, 1946.

The anatomic diagnosis at autopsy was (*a*) retinoblastoma (primary in the right eye); (*b*) tumor invasion of the left eye, optic nerve, meninges and cerebellum, and (*c*) internal hydrocephalus.

CASE 13.—E. R. was admitted to the Institute of Ophthalmology on June 11, 1947 with a history that in March 1946, the right eye had been enucleated for retinoblastoma. Postoperative radiation therapy was given. On admission the patient had symptoms and signs of intracranial extension, and she was transferred to Babies Hospital, New York, for terminal care. She died on July 13, 1947.

The anatomic diagnosis at autopsy was (*a*) retinoblastoma of the right eye; (*b*) secondary retinoblastoma in the optic chiasm, optic nerves, hypothalamus, third ventricle and subarachnoid space; (*c*) internal hydrocephalus, secondary, and (*d*) compression of the hypothalamus and cerebral peduncles, corpora striata, thalamus and optic system.

CASE 14.—N. J. was first seen in the Institute of Ophthalmology on Sept. 4, 1947 with a history that at the age of 1½ years she had complained of poor vision in the right eye. Eight months prior to her admission the right eye became red and painful. Examination revealed retinoblastoma of the right eye. The eye was enucleated on September 4. The visual fields revealed left temporal hemianopsia. On October 20 signs of cerebral involvement were noted, and on October 30 she was admitted to Babies Hospital, New York. She died November 14.

The anatomic diagnosis at autopsy was (*a*) retinoblastoma of the right eye; (*b*) extension of the tumor through the optic nerve to the base of the brain, and (*c*) internal hydrocephalus.

CASE 15.—M. M. was first seen in the Institute of Ophthalmology on March 18, 1947 with a history that two months previously the mother had noticed a squint. Examination with the patient under anesthesia revealed bilateral retinoblastoma, and the right eye was enucleated on March 25. Roentgen irradiation of the left eye was begun. On Jan. 19, 1948 the patient was readmitted with signs of intracranial involvement. She died on Feb. 20, 1948.

The anatomic diagnosis at autopsy was (*a*) retinoblastoma, bilateral; (*b*) extension of the retinoblastoma into the left optic nerve, chiasm, leptomeninges, cranial nerves and spinal roots, brain and spinal cord; (*c*) extension of the retinoblastoma into the third ventricle, and (*d*) marked dilatation of the lateral ventricles.

CASE 16.—J. W. was admitted to the Institute of Ophthalmology on Oct. 21, 1947, with a history that six or seven months previously the appearance of the right eye had been peculiar and enucleation had been advised. Permission for this was refused. Examination revealed retinoblastoma of the right eye, and the eye was enucleated on October 24. On April 5, 1948 recurrence was noted in the right orbit. On April 9 exenteration of the right orbit was done. On June 2 a mass was present in the lateral wall of the orbit and in the lateral aspect of the right side of the mandible. On June 13 a mass was present on the left side of the mandible. On July 27 metastatic areas were palpable in the skull. The patient died on Nov. 19, 1948.

The anatomic diagnosis at autopsy was (*a*) retinoblastoma, primary in the right eye, and (*b*) metastases to the cranium, the left side of the mandible and surrounding tissue, the right side of the mandible, and the sternum, liver, testes, cervical lymph nodes, right eighth rib, right fibula, right ulna and tibia, both femurs, radiuses and humeri and the right clavicle.

CASE 17.—H. A. was first seen by the referring physician on Aug. 1, 1947, with a history that at the age of 6 months a white reflex was noted in the left pupil. Operation was advised, and consent was refused but was finally given on Nov. 13, 1947. On Feb. 11, 1948 a recurrence was noted in the left orbit, and on February 17 the left orbit was exenterated. On February 24 there was evidence

of tumor in the right eye, and the patient was referred to the Institute of Ophthalmology for palliative radiation therapy. On July 6 an abdominal mass was discovered and the patient was admitted to Babies Hospital, New York. On July 22 salpingo-oophorectomy (right side) was done, and the pathologic diagnosis was metastatic retinoblastoma. The postoperative course was downhill, and the patient died on November 27.

The anatomic diagnosis at autopsy was retinoblastoma, bilateral, with spread to the cranium; cerebral dura; epidural space of the spinal cord in the cervical and lumbar regions; retroperitoneal nodes; left femur; right radius and ulna; ribs; uterus; left iliac crest; liver; right ovary, and hilar, perivesicular, left infraclavicular and axillary lymph nodes.

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ASYMMETRIC EXOPHTHALMOS

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THE PATIENT who has proptosis of one eye often presents a difficult diagnostic problem, of interest not only to the ophthalmologist, but also to the neurosurgeon and the clinician. That the entire problem of exophthalmos is complex is substantiated by the voluminous literature on the subject. There are many perplexing gaps in the present knowledge of exophthalmos. What is the mechanism or mechanisms of exophthalmos in exophthalmic goiter? What is the exact relationship between the thyroid and the pituitary glands? Why, if exophthalmic goiter is a systemic disease, should proptosis occasionally be apparently limited clinically to one side? Many investigators have shed considerable light on these and other questions, but there is little general agreement on many phases of this problem.

The differential diagnosis of asymmetric exophthalmos is hampered by the lack of a "yardstick" by which to compare the incidence and degree of proptosis in the numerous etiologic conditions encountered. In this paper we shall attempt to offer such a diagnostic aid. We shall present evidence that the exophthalmos of exophthalmic goiter is essentially a bilateral process, even though clinical appearances render the diagnosis of "unilateral exophthalmos" probable. The incidence, distribution and degree of asymmetry of exophthalmos will be compared in exophthalmic goiter and in proptosis caused by various neoplastic and other non-neoplastic disorders. In this paper, emphasis is placed on the differential diagnosis of the exophthalmos of exophthalmic goiter and that of other conditions causing proptosis.

MATERIAL AND METHOD

Records of the Mayo Clinic covering a ten year period were used as source material. All cases coded under exophthalmos were reviewed. Such cases were consecutive and unselected and included cases of exophthalmos from all causes

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Abridgment of a thesis submitted by Dr. Drescher to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Ophthalmology.

available from the records. From this group were separated those cases showing an asymmetric exophthalmos conforming to certain criteria of unilaterality that were established. These selected cases were subjected to statistical review, and the data were assembled, as shown in the accompanying table and charts. To furnish a control series, exophthalmometric readings were taken on 100 subjects for whom past or present causes of exophthalmos could be excluded. All measurements were taken with the Hertel exophthalmometer. This group was unselected and represented subjects of various age groups, body types, races and types of refractive errors.

Normal Exophthalmometric Measurements.—Exophthalmometric measurements of normal subjects must, of necessity, be expressed as a mean within a range. As persons vary in height and weight, so do they differ in the degree of prominence of their eyes. Variations occur in exophthalmometric readings taken on the same subject by the same observer or group of observers because of differing individual technics, variations in time of day or interorbital settings of the instrument used or differences in the type of instrument used or in calibration between several instruments of the same type.

Records of exophthalmometric measurements of normal eyes are scarce in the literature. The prominence of the eyes is generally expressed in millimeters and represents the distance in the anteroposterior plane between the temporal edge of the orbit and the summit of the cornea. An average of 12 to 14 mm. was obtained for 200 normal persons, as published in "The American Encyclopedia and Dictionary of Ophthalmology."[1] Ruedemann[2] measured 1,000 subjects and obtained readings of 14 to 20 mm. Wagener[3] found that in 80 per cent of 200 persons the measurements were between 15 and 20 mm., with a range of 11 to 24 mm. for the entire group. Brain and Turnbull,[4] in an unspecified number of normal subjects, found an average reading of 12.5 mm., with a maximum of 16 mm. Soley[5] measured 65 normal persons. He found a mean of 15.9 mm. and a range of 11.5 to 20 mm. In our series of 100 normal subjects the mean was 17.3 mm., with a range of 10 to 24 mm. (chart 1).

Rundle[6] placed the maximal normal amount of asymmetry of the two eyes at about 3 mm. The maximal degree of asymmetry in our control series of normal subjects was 2 mm., with a mean asymmetry of 0.24 mm. Ruedemann[2] also found 2 mm. as the maximal normal asymmetry of the eyes.

A subject with previous readings of 16 mm. may show up to 6 mm. of exophthalmos and the values still be considered within the normal range. From

1. The American Encylopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1915, vol. 7, p. 4851.

2. Ruedemann, A. D.: Exophthalmos, Cleveland Clin. Quart. **4**:66-75 (Jan.) 1937.

3. Wagener, H. P.: Exophthalmos in Horner's Syndrome, Tr. Am. Ophth. Soc. **31**:166-175, 1933.

4. Brain, W. R., and Turnbull, H. M.: Exophthalmic Ophthalmoplegia, with a Pathological Report on Ocular Muscles and Thyroid Glands, Quart. J. Med. **7**:293-323 (April) 1938.

5. Soley, M. H.: Exophthalmos in Diseases of the Thyroid, California & West. Med. **60**:64-68 (Feb.) 1944.

6. Rundle, F. F.: Some Observations on Exophthalmos, West. J. Surg. **55**:578-583 (Nov.) 1947.

this it is apparent that exophthalmos is impossible to diagnose unless (1) it is obvious bilaterally, (2) previous readings have been taken on the patient or (3) an asymmetry of the eyes of more than 2.5 mm. exists. Readings between 22 and 24 mm. should be viewed with suspicion as indicating an underlying pathologic condition, and those beyond 24 mm. probably can be considered almost universally abnormal.

Criteria for Selection of Our Cases.—As previously mentioned, our series of control exophthalmometric measurements showed a mean of 17.3 mm., with a range of 10 to 24 mm. For only 3.5 per cent of the subjects did the measurements exceed 22 mm. Of the total series, 92 per cent of measurements lay between 14

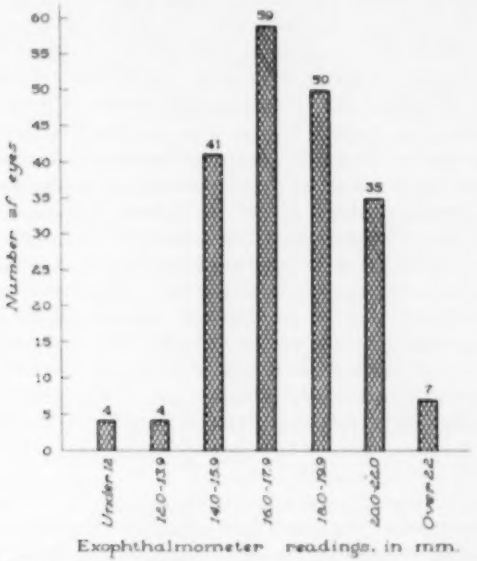

Chart 1.—Distribution of exophthalmometric measurements of 200 normal eyes (100 subjects).

and 22 mm. We place the upper limit of normal at 22 mm., although it must be conceded that an occasional patient will show a normal prominence of the eyes up to 24 mm.

Two millimeters of asymmetry between the eyes was the maximum found. Accordingly, allowing 0.5 mm. for error, a figure of 2.5 mm. was selected as the maximal normal asymmetry of the eyes.

The cases included in our series therefore conform to the following criteria of unilaterality: 1. Asymmetry between the eyes must be 2.5 mm. or more. 2. The less prominent of the two eyes must lie within the normal range of prominence, that is, between 10 and 22 mm., as measured by the Hertel exophthalmometer. These criteria insure the rejection of cases of obviously bilateral exophthalmos and of normal cases, although perhaps at the expense of not including in the series a

few cases of minimal exophthalmos. So far as could be determined, all readings were taken with the Hertel exophthalmometer. Of necessity, the readings of a number of observers were utilized. In any individual case, the figures taken were the maximum recorded during the patient's stay under observation.

COMMON CAUSES OF ASYMMETRIC EXOPHTHALMOS

A glance at the table will reveal more than sixty causes of proptosis. The majority of cases, however, fall into a group representing about a dozen causes. Pfeiffer [7] found that two thirds of his cases were grouped under twelve diagnoses. In approximately 60 per cent of the present series the exophthalmos was found to be due to six disorders: exophthalmic goiter, 25 per cent; meningioma, 11 per cent; hemangioma, 7 per cent; mucocele, 7 per cent; arteriovenous aneurysm, 6 per cent, and malignant lesions of the paranasal sinuses, 4 per cent.

Exophthalmic Goiter.—There is a growing tendency to differentiate the exophthalmos of exophthalmic goiter into two varieties. The first type occurs in the so-called classic toxic diffuse goiter (Graves's disease). Here the emphasis is placed on the constitutional manifestations of the disease, with the ocular role secondary. It is generally stated that in this condition the exophthalmos rarely exceeds 3 mm. and that asymmetry of exophthalmos is uncommon.[6] The second type of exophthalmos is described as occurring in a many-named syndrome, characterized by persistent or progressive exophthalmos, generally associated with palsies of extraocular musculature and a moderately elevated, normal or depressed basal metabolic rate. The exophthalmos may increase when the metabolic rate is controlled by medical treatment or by thyroidectomy. In some instances medical or surgical treatment may precede the increase of exophthalmos.

Jensen [8] applied the name "malignant exophthalmos" to the second type. Brain [9] stated preference for the name "exophthalmic ophthalmoplegia," while Thomas and Woods [10] employed the term "progressive exophthalmos after thyroidectomy." Means, in his earlier paper with Hertz and Williams,[11] stated that he preferred the title "Graves' dis-

7. Pfeiffer, R. L.: Roentgenography of Exophthalmos, with Notes on the Roentgen Ray in Ophthalmology, Tr. Am. Ophth. Soc. **39**:492-560, 1941.

8. Jensen, V. A.: Malignant Exophthalmus After Strumectomy, Acta ophth. **18**:1-20, 1940.

9. Brain, W. R.: Exophthalmic Ophthalmoplegia, Tr. Ophth. Soc. U. Kingdom **57** (pt. 1):107-115, 1937.

10. Thomas, H. M., Jr., and Woods, A. C.: Progressive Exophthalmos Following Thyroidectomy, Bull. Johns Hopkins Hosp. **59**:99-113, 1936.

11. Means, J. H.; Hertz, S., and Williams, R. H.: Graves' Disease with Dissociation of Thyrotoxicosis and Ophthalmopathy, West. J. Surg. **49**:493-498 (Sept.) 1941.

ease with dissociation of thyrotoxicosis and ophthalmopathy," although in his latest text [12] he employed the term "hyperophthalmopathic Graves' disease." This entity corresponds to the "thyrotropic type of exophthalmos" of Mulvany [13] and the "ophthalmic type" of Rundle and Wilson.[14] Hereafter, in this report the term "hyperophthalmopathic Graves's disease" will be used when referring to this syndrome.

The detection of those patients in whom pronounced exophthalmos will conceivably develop during medical treatment or after thyroidectomy is usually impossible, although the potentiality may be suspected. A careful evaluation of the ocular signs and the recognition of certain differential features are necessary in order to distinguish this group from that with the usual exophthalmos of exophthalmic goiter. These points have been summarized by Woods [15] as follows: Early in the course of the disease the degree of exophthalmos may be slight, but usually it progresses to a moderate or extreme degree. Asymmetry of the proptosis is fairly common. Whether the exophthalmos is slight or extreme, it is generally associated with chemosis, edema of the lids, diplopia or frank tropias, epiphora, photophobia and inability of the observer to reduce the exophthalmos appreciably by pressure on the globes.

Histologically, the striated orbital musculature in this condition may show pronounced changes. These changes were described by Burch [16] in 1929 and were subsequently studied carefully by Naffziger,[17] Friedenwald [18] and Thomas and Woods.[19] The changes described by these investigators are essentially those of hypertrophic myositis, namely, tremendous hypertrophy, interstitial fibrosis and edema of the muscle with focal lymphocytic infiltration. Dobyns [19] showed histologic

12. Means, J. H.: The Thyroid and Its Diseases, ed. 2, Philadelphia, J. B. Lippincott Company, 1948.

13. Mulvany, J. H.: The Exophthalmos of Hyperthyroidism: A Differentiation in the Mechanism, Pathology, Symptomatology, and Treatment of Two Varieties, Am. J. Ophth. **27**:589-612 (June); 693-712 (July); 820-832 (Aug.) 1944.

14. Rundle, F. F., and Wilson, C. W.: Asymmetry of Exophthalmos in Orbital Tumour and Graves's Disease, Lancet **1**:51-52 (Jan. 13) 1945.

15. Woods, A. C.: The Ocular Changes of Primary Diffuse Toxic Goitre: A Review, Medicine **25**:113-153 (May) 1946.

16. Burch, F. E.: The Exophthalmos of Graves' Disease, Minnesota Med. **12**:668-675 (Nov.) 1929.

17. Naffziger, H. C.: Pathologic Changes in the Orbit in Progressive Exophthalmos, with Special Reference to Alterations in the Extra-Ocular Muscles and the Optic Disks, Arch. Ophth. **9**:1-11 (Jan.) 1933.

18. Friedenwald, J. S.: Orbital Myositis and Choked Disc in Exophthalmic Goitre, Ann. Surg. **96**:995-997 (Dec.) 1932.

19. Dobyns, B. M.: Exophthalmos and Tissue Changes in the Guinea Pig Following Administration of the Thyroid Stimulating Hormone of the Pituitary Gland, West. J. Surg. **54**:411-425 (Nov.) 1946.

evidence of edema and cellular infiltration of the orbit in experimental animals given thyrotropic hormone. Rundle and Pochin,[20] however, showed pathologic changes in orbital tissue of thyrotoxic patients even when ocular signs were absent; the question therefore arises whether hyperophthalmopathic Graves's disease is merely the same disease entity as the classic Graves's disease with more advanced orbital changes.

The pathogenesis of exophthalmos in exophthalmic goiter is obscure. Means [21] expressed the belief that the ocular syndrome is only a part of a generalized disturbance of water balance and electrolytes. Since the orbit is closed in all directions except anteriorly, any increase in its contents is partially expressed as proptosis. In Daniels' [22] opinion, the original cause is a disturbance of the adrenal glands or gonads, the anterior lobe of the pituitary gland being activated indirectly through the hypothalamus. As Woods [15] pointed out, the occurrence of exophthalmos in patients with low basal rates and the frequent improvement of the patient after administration of desiccated thyroid and iodine indicate that the condition is not associated with hyperthyroidism and thyrotoxicosis, or with an increased amount of normal thyroxin. On the contrary, Woods expressed the opinion that the condition may be due to hypothyroidism or a deficiency of normal thyroxin. Marine and Rosen [23] hypothesized that the exophthalmos of hyperophthalmopathic Graves's disease may be different from that of primary toxic goiter, the latter type of exophthalmos being produced more particularly by edema of the orbital contents and the former by organic hyperplasia of the orbital contents.

Aird [24] came to somewhat the same conclusion after his work on experimental exophthalmos in animals produced by extract of the anterior lobe of the pituitary. He stated the belief that in hyperophthalmopathic Graves's disease the cause lay in a degenerative and fibrotic myopathy, due to the patient's failure to establish a proper endocrine adjustment after operation.

It was formerly commonly accepted that, with the exception of the hyperophthalmopathic group, the exophthalmos of exophthalmic goiter becomes less after the basal metabolic rate has been controlled. Recent

20. Rundle, F. F., and Pochin, E. E.: The Orbital Tissues in Thyrotoxicosis: A Quantitative Analysis Relating to Exophthalmos, Clin. Sc. **5**:51-74, 1944.

21. Means, J. H.: The Diagnosis and Treatment of Hyperthyroidism, Canad. M. A. J. **43**:509-513 (Dec.) 1940.

22. Cited by Woods.[15]

23. Marine, D., and Rosen, S. H.: Exophthalmos in Thyroidectomized Guinea Pigs by Thyrotropic Substance of Anterior Pituitary, and the Mechanism Involved, Proc. Soc. Exper. Biol. & Med. **30**:901-903 (March) 1933.

24. Aird, R. B.: Experimental Exophthalmos and Associated Myopathy Induced by the Thyrotropic Extract, Arch. Ophth. **24**:1167-1178 (Dec.) 1940.

studies by Soley [25] and by Dobyns and Haines [26] indicate, however, that an actual increase of exophthalmos is the commoner result. Dobyns and Haines demonstrated a slight increase of exophthalmos in the majority of patients after treatment with iodine, after thyroidectomy, during postoperative myxedema and during treatment of exophthalmic goiter with thiouracil.

Various hypotheses have been formulated to account for the exophthalmos of Graves's disease. Woods used the following grouping of the more prominent hypotheses: (1) hypertrophy of the orbital contents; (2) relaxation of the striated extraocular musculature; (3) contraction of the smooth muscle of the orbit or lids; (4) simple edema of the orbital contents; (5) dilation of the orbital blood vessels; (6) hypertrophic myositis of the orbital muscles; (7) action on the orbital contents of a hormone of the anterior lobe of the pituitary gland.

1. Hypertrophy of the Orbital Contents: Von Basedow [28] originally suggested that exophthalmos of exophthalmic goiter was caused by hypertrophy or hyperplasia of the orbital contents, especially the fat. Smelser [27] analyzed the orbital contents in a series of cases of clinical and experimental exophthalmos. He found an actual hyperplasia of orbital contents, in which the fat played a prominent role. Specifically, Smelser demonstrated a 30 per cent increase over the control series of the weight of the orbital contents of guinea pigs which had been thyroidectomized and treated with extract of the anterior lobe of the pituitary. He found a 100 per cent increase in the fatty connective tissue, a 40 per cent increase in the dorsal lacrimal gland and a 22 per cent increase in the size of the extraocular muscles.

2. Relaxation of the Striated Extraocular Musculature: Cooper,[28] in 1849, and Fisher,[29] in 1921, both suggested that relaxation of the four rectus muscles was a contributing factor to the development of exophthalmos. Mulvany [18] also expressed the belief that relaxation of the striated extraocular musculature was a factor in the exophthalmos of his thyrotoxic group. He described a "thyrotoxic myasthenia" which by organic changes produces weakening and relaxation of the orbital

25. Soley, M. H.: Exophthalmos in Patients with Various Types of Goiter, Arch. Int. Med. **70**:206-220 (Aug.) 1942.

26. Dobyns, B. M., and Haines, S. F.: Changes in the Prominence of the Eyes in Various Thyroid States, J. Clin. Endocrinol. **6**:633-642 (Sept.) 1946.

27. Smelser, G. K.: Experimental Production of Exophthalmos Resembling That Found in Graves' Disease, Proc. Soc. Exper. Biol. & Med. **35**:128-130 (Oct.) 1936.

28. Cooper, W. W.: On Protrusion of the Eyes in Connexion with Anaemia, Palpitation, and Goitre, Lancet **1**:551-554 (May 26) 1849.

29. Fisher, C., in discussion on Parker, W. R.: Double Luxation of the Eyeballs in a Case of Exophthalmic Goiter, Tr. Am. Ophth. Soc.; Arch. Ophth. **51**:1 (Jan.) 1922.

striated muscles. In his opinion, these changes, together with contraction of the orbital smooth muscle, are responsible for exophthalmos in the thyrotoxic group.

3. Contraction of the Smooth Muscle of the Orbit or Lids: This hypothesis postulates that exophthalmos caused by thyroid disease is contributed to by two factors: (1) excitation of cervical sympathetic nerves with contraction of smooth muscle fibers in the orbit, and (2) orbital edema caused by venous congestion. Hesser,[30] in 1913, showed that in man Müller's muscle is vestigial and could not alter the position of the globe and that compression of the small venules in the muscle could not produce orbital venous stasis because of the free and extensive anastomosis with the facial veins.

Landström,[22] in 1907, described a smooth muscle of the anterior segment of the eye. In his opinion, contraction of this muscle caused proptosis. Hesser [30] and Troell [22] were unable to confirm the presence of this smooth muscle and expressed the belief that Landström was in reality describing a portion of Müller's orbital muscle.

Rundle [6] did not attribute proptosis in man to stimulation of the cervical sympathetic nerves. In the anesthetized dog such stimulation of the cervical sympathetic nerves resulted in from 4 to 5 mm. of proptosis, caused by a wave of contraction in the muscular lateral wall of the orbit, with consequent diminution of volume of orbital space. This exophthalmos thus is due not to an increase of orbital contents but, rather, to a reduction of orbital volume. In man the orbital walls are completely bony and, though vestigial rudimentary smooth muscle may sometimes be found in the region of the anterior orbital fissure, stimulation of the sympathetic trunk with an exophthalmometer in place, as during operations on the neck, does not result in protrusion of the globes.[31]

4. Simple Edema of the Orbital Contents: Sattler,[22] in 1911, expressed the belief that simple orbital edema was the cause of exophthalmos of toxic goiter. He pointed out the similarity to edema of the lids, secondary to capillary dilatation. He showed simple edema of the orbital contents histologically and stated the belief that a toxin produced a selective orbital edema. Subsequent studies have confirmed the statement that edema is a factor in the increased bulk of orbital contents. Paulson [32] administered pituitary extract containing a potent thyrotropic

30. Hesser, C.: Der Bindegewebsapparat und die glatte Muskulatur der Orbita beim Menschen in normalem Zustande, Anat. Hefte **49**:1-302, 1913.

31. Benedict, W. L.: Concerning Exophthalmos, with Special Reference to Goiter, South. M. J. **31**:321-325 (March) 1938.

32. Paulson, D. L.: Experimental Exophthalmos and Muscle Degeneration Induced by Thyrotropic Hormone, Proc. Staff Meet., Mayo Clin. **14**:828-832 (Dec. 27) 1939.

factor to guinea pigs. He found a retrobulbar edema, more pronounced in thyroidectomized animals than in intact animals. He attributed the proptosis to this edema of orbital contents. Galli-Mainini [33] hypothesized that the patient who has thyrotoxicosis is maintaining his water balance at the upper limit of capacity.

5. Dilatation of the Orbital Blood Vessels: This hypothesis assumes that thyrotoxicosis produces widespread disturbance of vascular nerve control, including the cervical sympathetic system. Because of this, it is believed that dilatation of the carotid and orbital vessels occurs, resulting in proptosis. This hypothesis has several shortcomings: 1. Not all cases of exophthalmic goiter with exophthalmos show ocular congestive phenomena. 2. Vasodilatation of the orbital contents alone cannot account for the histologic picture of hypertrophy and hyperplasia. 3. The orbital veins are free of valves and have adequate anterior and posterior communications.

6. Hypertrophic Myositis of the Orbital Muscles: This factor was advanced by Naffziger and Jones [34] as contributing to the exophthalmos of thyrotoxicosis, particularly in progressive exophthalmos following thyroidectomy. Woods [18] pointed out that this hypothesis, again, does not seem to fit the entire picture, since such fibrosis and hypertrophy of the extraocular muscles are observed inconstantly, are present in only a few patients and may be entirely absent even in severe progressive exophthalmos.

7. Action of a Hormone of the Anterior Lobe of the Pituitary on the Orbital Contents: The concept of the relation of exophthalmos of toxic diffuse goiter to a hormone of the anterior lobe of the pituitary gland is based on a series of laboratory experiments. Loeb and Friedman,[35] among other investigators, produced by the injection into animals of an extract of the anterior lobe of the pituitary the picture of a thyrotoxicosis which included exophthalmos in a substantial percentage.

Marine and Rosen [29] investigated this experimental exophthalmos and its relation to hyperthyroidism. By injecting extract of the anterior lobe of the pituitary, they could produce exophthalmos in rabbits, particularly if thyroidectomy had been previously performed. The

33. Galli-Mainini, C.: Exophthalmometric Measurements in Patients with Thyroid Disease, with Some Discussion of Their Significance, Ann. Int. Med. **16**:415-426 (March) 1942.

34. Naffziger, H. C., and Jones, O. W., Jr.: The Surgical Treatment of Progressive Exophthalmos Following Thyroidectomy, J. A. M. A. **99**:638-642 (Aug. 20) 1932.

35. Loeb, L., and Friedman, H.: Exophthalmos Produced by Injections of Acid Extract of Anterior Pituitary Gland of Cattle, Proc. Soc. Exper. Biol. & Med. **29**:648-650 (Feb.) 1932.

development of exophthalmos could be prevented by administration of thyroxin and iodine or by extirpation of the cervical sympathetic nerve supply. They concluded that the exophthalmos was produced by stimulation of the cervical sympathetic fibers and contraction of Müller's orbital muscle. In their opinion, the development of exophthalmos was dependent on a relative thyroid deficiency.

The questionable part that the cervical sympathetic nerves and Müller's orbital muscle played in this picture was made clear by the experimental work of Smelser,[27] in 1936. He concluded that there was a similarity between the experimental exophthalmos produced by the hormone of the anterior lobe of the pituitary and the clinical exophthalmos of thyrotoxicosis. He did not believe that venous stasis, contraction of smooth muscle or sympathetic stimulation played a part in either process. As previously stated, he found an increase in orbital contents contributed to by edema, an increase of fat and increased volume of the striated muscles. The increase of orbital tissue was somehow related to the action of the anterior lobe of the pituitary, but whether through thyrotropic hormone or not remains unknown.

Dobyns[19] injected a thyroid-stimulating hormone of the anterior lobe of the pituitary body into guinea pigs. He produced a pronounced exophthalmos regardless of the presence or absence of the thyroid gland or the testes. He described a connective tissue reaction throughout the body and rapid depletion of fat deposits, with replacement by edema and connective tissue. In his opinion, the orbital changes are part of this generalized picture. Histologically, he showed that these changes in fat and connective tissue are characterized by the presence of edema and the infiltration of many granulocytes, lymphocytes and tissue macrophages.

Mulvany expressed the belief that hyperthyroidism is of three distinct types: a thyrotoxic type, associated with hyperthyroidism and sympathetic stimulation; a thyrotropic type, related to the anterior lobe of the pituitary gland, and a thyropathic variety, including thyroid disease, such as malignant lesions, thyroiditis and lymphadenoid goiter. Exophthalmos occurs only in the first two types, and in Mulvany's opinion they can be sharply differentiated. He expressed the belief that the exophthalmos of thyrotoxicosis is caused by the combination of spastic contraction of Landström's and Müller's orbital muscles together with a so-called myasthenia of the extraocular muscles. He described the characteristics of the thyrotoxic type as normal orbital contents, absence of intraorbital edema, spastic retraction of the lids and degeneration of the extraocular muscles of a kind which differs sharply from that found in the thyrotropic type.

Mulvany attributed the exophthalmos of his thyrotropic type to an increase of orbital contents with hypertrophy and degeneration of the orbital striated musculature. These orbital changes result in increased orbital pressure, with resulting proptosis. The primary differential points present in the thyrotropic type and absent in the thyrotoxic variety were stressed by Mulvany. These consist of the subjective phenomena, the incidence of asymmetry of exophthalmos, the absence of true spasm of the lids, the frequently higher degree of proptosis, difficulty in reduction of exophthalmos by pressure on the globe, chemosis of the conjunctivas and edema of the eyelids.

Benedict [36] expressed the belief that the exophthalmos of exophthalmic goiter is sometimes delayed, following by several months a subclinical episode of mild exophthalmic goiter productive of no noticeable general symptoms.

Hemangioma.—This tumor is generally considered the commonest primary tumor of the orbit. It is probably congenital in origin but may not appear until the fifth decade of life. The hemangioma is radiosensitive, is often encapsulated and is considered benign. The amount of connective tissue stroma varies, some tumors being cavernous or cystic and others rather firm. Several characteristics of this tumor are worth emphasis [7]: 1. It does not interfere with ocular rotations. 2. When located deep in the orbit, it commonly gives roentgenographic evidence of increased intraorbital pressure. 3. The amount of exophthalmos produced is variable. These variations are, of course, reflections of the size of the tumor, which may be altered in size spontaneously by changes in the orbital venous drainage, such as those produced by compression of the jugular vein incident to crying, straining or coughing. The clue to a hemangioma of the orbit may occasionally be seen in a similar lesion of the eyelid or subconjunctival space. An acute increase in the amount of exophthalmos is occasionally seen as the result of thrombosis of vessels involved in a hemangioma.

Pseudotumor.—The pseudotumor is a chronic cellulitis or granulomatous process of unknown origin. The orbital tissues show microscopic evidence of chronic inflammation within a stroma of fibrous tissue. Foci of lymphocytes are present throughout, and lymph follicles with germinal centers have been described.[7]

Reese [37] described the following differential points between pseudotumor and real tumor of the orbit: 1. Pseudotumor tends to occur in the

36. Benedict, W. L.: Diagnosis of Orbital Tumors: Address of the Guest of Honor, J. A. M. A. **126**:880-884 (Dec. 2) 1944.

37. Reese, A. B.: Orbital Tumors and Their Surgical Treatment, North Carolina M. J. **1**:583-592 (Nov.) 1940.

fourth and fifth decades; primary tumor, earlier in life. 2. The development of exophthalmos of pseudotumor is relatively rapid as compared with that for primary tumor, with which exophthalmos is usually slow in development. 3. Primary tumor is never bilateral; pseudotumor is bilateral in one third of the cases, an interval of four to nine months occurring before involvement of the second eye. 4. A real tumor (primary or metastatic) often shows roentgenographic changes of the orbital bones; the pseudotumor, characteristically produces none. 5. Primary tumor generally causes no pain or edema of the conjunctiva or lids; pseudotumor causes pain and edema in 50 per cent of cases.

Mucocele or Pyocele (Retention Cyst of Paranasal Sinuses).—This lesion is a very common cause of proptosis of one eye. Usually the cyst produces a firm exophthalmos, with the globe displaced forward and temporally or inferiorly. The roentgenogram usually shows a characteristic picture—a defect or hiatus of the wall of the clouded sinus, in which a part of the outline of the cyst may often be seen.

Meningioma.—This is a slow-growing tumor, considered by many observers to be usually benign. It arises in the cell clusters of the arachnoid and has several characteristic sites, with corresponding syndromes: (1) meningioma of the optic nerve; (2) meningioma of the sphenoid ridge; (3) meningioma of the tuberculum sellae, and (4) meningioma of the olfactory groove. The last two types do not produce exophthalmos and are not discussed in this paper.

Meningiomas of the optic nerve usually cause early loss of vision with optic nerve atrophy or papilledema and proptosis. These tumors lie in the muscle cone at the apex of the orbit, surrounded by the extraocular muscles. Because of this, impairment of ocular rotation is an early suggestive sign. The bones of the orbit, lying close, are often infiltrated, with resultant hyperostosis. The close relationship to the optic canal and the superior orbital fissure favors spread into the cranial cavity.

Meningiomas of the sphenoid ridge may be conveniently divided into three groups, depending on which portion of the sphenoid ridge is involved. Those arising on the inner third of the sphenoid crest involve the optic canal, producing optic nerve atrophy or papilledema and exophthalmos. Those arising on the middle third of the ridge may produce large hyperostoses and exophthalmos without subjective symptoms. Involvement of the outer third of the sphenoid ridge usually implicates the temporal fossa and may produce bulging of the temporal area.

The hyperostoses of contiguous bone are attributed to growth of the tumor into the haversian canal system of the bone, with resultant osteoclastic proliferation. The presence of such hyperostoses is of para-

mount importance when evident on the roentgenogram. It should be borne in mind, however, that other lesions, particularly vascular tumors, characteristically produce hyperostoses.[38]

Elsberg, Hare and Dyke[39] reported a series of 807 verified cases of intracranial neoplasm. In 15 cases (1.9 per cent) there was marked proptosis of one eye. In 10 (*67* per cent) of these 15 cases the proptosis was caused by meningioma. Elsberg and associates reported that the exophthalmos was most frequent on the left side in females (in 7 of 8) and on the right side in males (in 5 of 7). In the 17 cases of dural meningioma included in our series, no such predilection for one side could be found on the basis of sex, the exophthalmos predominating in females on both the right and the left side by a ratio of almost 2:1. Elsberg, Hare and Dyke expressed the belief that the proptosis was usually caused by involvement of the orbital walls, intraorbital extension of the tumor or increase of orbital pressure transmitted from the cranial cavity through the superior orbital fissure. They found no evidence which would attribute the exophthalmos to compression of the cavernous sinus or the ophthalmic veins, with resultant venous stasis. The series of Reese and our series include cases of meningioma, whether it was primary in the orbit or intracranial, since it is often impossible to designate the origin, either clinically or at operation. Reese indicated that of the 13 cases of meningioma in his series the tumor was primary in the orbit in 4 and in the cranial cavity in 7, and that in 2 the origin was not determined.

Dermoid and Epidermoid Cysts.—These congenital cysts are usually located in the anterior portion of the orbit. However, they may lie deep in the orbit or extend posteriorly along the bony walls to a retrobulbar position, thus giving rise to proptosis. The roentgenogram is usually helpful in diagnosis, showing well defined bony defects with increased density peripherally.

Glioma of the Optic Nerve or Chiasm.—Reese[37] considered this a rare tumor, although Pfeiffer[7] did not agree, finding 7 cases of the tumor (3.5 per cent) in his series of 200 cases. The present series of 177 cases includes 3 cases (1.7 per cent). The glioma of the optic pathways is slow growing and of a relatively low degree of malignancy. There is variation of the cell type, the majority being either astrocytomas or oligodendrocytomas. Visual loss commonly precedes the exophthalmos. The roentgenogram is invaluable in diagnosis and may

38. Benedict, W. L.: Surgical Treatment of Tumors and Cysts of the Orbit, Am. J. Ophth. **32** (pt. 1):763-773 (June) 1949.

39. Elsberg, C. A.; Hare, C. C., and Dyke, C. G.: Unilateral Exophthalmos in Intracranial Tumors with Special Reference to Its Occurrence in the Meningiomata, Surg., Gynec. & Obst. **55**:681-699 (Dec.) 1932.

show enlargement of the optic canal or deformity of the sella turcica if the chiasm is involved. In children this tumor should be differentiated from retinoblastoma and neurofibromatosis.

Neurofibromatosis.—This condition is generally considered the commonest of the neurogenic tumors of the orbit. If offers many characteristics which help in establishing the diagnosis. Among these are the pigmentation of the skin, the multiple small neurofibromas or pigmented nevi and the roentgenogram, which may show effects in the adjacent orbital bones. These tumors may involve not only the orbit but the lids, face, cranium and intraocular structures.

Mixed Tumor of the Lacrimal Gland.—Reese [37] stated that 95 per cent of tumors of the lacrimal gland are of the mixed ectodermal and mesodermal type. Pfeiffer [7] considered them congenital. The average age of patients in Reese's series at the time of discovery of the tumor was 45 years. In the cases reviewed by us the average age was also 45 years. These tumors characteristically arise during or after middle age and may produce roentgenographically visible changes, such as localized bony defects of the orbital wall or hyperostoses. Sanders [40] pointed out that they must be considered malignant because of their marked tendency to recur locally, with destruction of the orbital bones, and their tendency to metastasize (33 per cent) or extend intracranially (42 per cent). This is particularly true of the cylindroma, which shows a decided tendency to invade bone.

Malignant Tumors of the Nasopharynx.—In Reese's [37] opinion, these tumors are a common cause of exophthalmos from a source outside the orbit. His classification includes transitional cell carcinoma, lymphoepithelioma, lymphosarcoma and a group too anaplastic for identification. The site of origin is usually in the posterior portion of the nasopharynx. These tumors enter the orbit through the superior orbital fissure, having accompanied the internal carotid artery from the carotid groove.

Malignant Tumors of the Paranasal Sinuses.—These tumors must be considered not uncommon. The present series includes 7 cases (4.0 per cent). Invasion of the orbit is by direct extension from the paranasal sinuses. The cell type corresponds in general to that of malignant lesions arising in the nasopharynx. Reese found the maxillary sinus the most frequent primary site. He pointed out that malignant lesions of the ethmoid sinuses probably produce exophthalmos in a large percentage of cases, because only the thin lamina papyracea separates the ethmoid sinuses from the orbit and also because of the frequent association of infection with malignant lesions of the ethmoid cells, with resultant orbital inflammation.

40. Sanders, T. E.: Mixed Tumor of the Lacrimal Gland, Arch. Ophth. **21**:239-257 (Feb.) 1939.

Arteriovenous Aneurysm.—The majority of arteriovenous aneurysms causing proptosis are traumatic and involve the internal carotid artery and the cavernous sinus. Such aneurysms, however, also arise spontaneously or as a result of inflammation in the region of the cavernous sinus. Typically the condition is characterized by pulsating exophthalmos and bruit over the orbit or skull. The pulsation, usually palpable, and often directly visible, is either of the globe or of dilated veins of the brow, lids or glabella. The veins of the retina, conjunctiva and lids may be enormously dilated. Pulsating exophthalmos may also be caused by a variety of other lesions, both intraorbital and extraorbital, among which are highly vascular tumors of the orbit, aneurysm of the ophthalmic artery in its intracranial or intraorbital portion, aneurysm of the interior carotid artery and varicosities of the orbital veins.

In 6 of the 11 cases of arteriovenous aneurysm which we reviewed, the lesion was caused by a connection between the cavernous sinus and the carotid artery; in 1 it was in the retrobulbar region, and in 4 the site was not specified. Of the total, the aneurysm was traumatic in origin in 8 and spontaneous in 3.

Hemangioendothelioma.—Although not a common tumor, it is felt that this neoplasm should be mentioned because of the scarcity of cases in the literature. We found 5 verified cases in the present series. Benedict [38] gave an incidence of 33 cases of hemangioendothelioma in his series of 3,190 tumors of the eye. He found them more frequent in the apex of the orbit than in other sites. This tumor varies in malignancy, is seldom encapsulated and rapidly invades the orbital tissues along nerve and blood vessel pathways. It is radioresistant and offers a poor prognosis.

COMMENT

The accompanying table is a compilation of the causes and incidences of exophthalmos as reported by several authors. The diagnoses have been divided into three categories: (1) exophthalmos due to neoplasm, (2) exophthalmos due to non-neoplastic conditions and (3) exophthalmos of unknown origin.

The data presented in the table are not intended to be comparable for the various authors, since dissimilar criteria were used by them in the selection of cases. Pfeiffer's [7] series represents exophthalmos of one or both eyes, while O'Brien and Leinfelder [41] included only cases of unilateral exophthalmos, the criteria for unilaterality not being given.

41. O'Brien, C. S., and Leinfelder, P. J.: Unilateral Exophthalmos: Etiologic and Diagnostic Studies in 82 Consecutive Cases, Am. J. Ophth. **18**:123-132 (Feb.) 1935.

Diagnosis	Pfeiffer [7]	Dandy [42]	Iba and Short [44]	Jackson [43]	Reese [37]	O'Brien and Leinfelder [31]	Drescher and Bonsnes [32]
I. Neoplasms							
Adamantinoma	..	..	..	..	..	1	..
Carcinoma, primary, of orbit							
Lacrimal gland	..	..	1	..	..	..	..
Mixed tumor of lacrimal gland	5	..	1	1	9	..	6
Unknown origin	..	1	..	..	..	..	2
Carcinoma of orbit, secondary to lesion of							
Breast	..	..	..	..	3	2	2
Cervix	..	..	..	..	..	..	1
Conjunctiva	..	..	..	..	..	2	..
Eyelids							
Basal cell	2	..	..	..	2	1	..
Squamous cell	..	..	..	..	1	..	..
Prostate	..	..	..	..	..	..	1
Stomach (via brain)	..	..	..	..	..	1	..
Thyroid	..	..	..	..	1	..	..
Tonsil	..	..	..	..	1	..	..
Unknown origin	..	..	..	..	2	..	..
Chondromyxoma	..	..	..	..	..	1	..
Dermoid and epidermoid	6	..	1	2	4	..	3
Fibroma	..	1	..	..	1	..	..
Glioma of optic nerve or chiasm	6	4	..	6	1	1	3
Hemangioendothelioma	..	..	..	..	..	..	3
Hemangioma	12	..	4	1	20	1	12
Lipoma	..	..	1	..	..	..	..
Lymphangioma	..	..	..	..	1	..	..
Malignant lesions of nasopharynx	..	..	..	..	19	..	..
Malignant lesions of orbit, secondary, other than carcinoma and sarcoma	..	..	..	..	2	..	..
Malignant lesions of paranasal sinuses	5	..	..	..	11	3	7
Melanoepithelioma of choroid, with orbital extension	2	..	..	..	2	..	1
Meningioma							
Dural	14	11	..	..	13	4	11
Of optic nerve sheath	..	1	..	1	..	..	1
Miscellaneous, unclassified							
Nose to orbit, via tear sac	..	..	..	..	1	..	..
Neoplasm of hard palate	..	..	..	..	1	..	..
Myeloma	1	..	..	..	..	..	..
Neoplastic diseases of the hemopoietic system							
Chloroma	..	..	..	..	1	..	..
Leukemia, all types	..	..	..	..	1	1	2
Malignant lymphoma	..	..	..	..	3	2	1
Undifferentiated tumors	..	..	..	..	..	2	..
Neurilemmoma	..	..	..	..	1	..	..
Neurofibroma	7	..	..	..	4	1	1
Neuroma	2	..	..	..	..	..	..
Osteoma	3	1	..	..	1	..	4
Sarcoma							
Primary in orbit	6	† 3	† 2	..	10	5	5
Secondary in orbit	..	1	..	..	1	3	2
Xanthomatosis	2	5	..	..	2	..	1
Total neoplasms	75	28	10	9	130	33	78
II. Non-neoplastic Lesions							
Arteriovenous aneurysm	6	..	..	..	..	3	11
Congenital colobomatous cyst	3	..	..	..	..	..	..
Craniostenosis	14	..	..	..	..	..	1
Cysts of orbit, varied types	1	1	1	..	..	..	..
Deformity or asymmetry of orbits	7	..	..	..	..	..	..
Emphysema of orbit	..	..	..	..	..	1	..
Exophthalmic goiter	12	..	..	..	..	7	45
Gumma	2	..	..	..	1	..	..
Hematoma							
Retrobulbar	..	..	..	..	3	4	..
Subdural	1	..	..	..	..	..	..
Inflammation of orbit, including abscesses, all causes	4	..	1	..	1	31	2
Iodized oil in orbit	1	..	..	..	..	..	..
Mikulicz disease	..	..	..	..	..	..	1
Mucocele	18	..	1	3	..	3	12
Myopia, axial	2	..	..	..	..	1	1
Oculomotor paralysis	9	..	..	..	..	..	..
Osteitis fibrosa cystica	1	..	..	..	1	..	..
Osteitis deformans	3	..	..	..	..	..	..
Pseudotumor	16	1	..	3	16	1	3
Sacculated aneurysm of internal carotid artery	4	..	..	..	..	..	..
Trichinosis	1	..	..	..	..	..	..
Zenker's waxy degeneration of rectus muscle	..	..	..	..	1	..	..
Total non-neoplastic lesions	105	2	3	6	23	46	76
III. Undiagnosed exophthalmos	20	..	..	..	..	3	23
Grand total	200	30	13	15	153	82	177

The data of Dandy,[42] Jackson [43] and Iles and Short [44] are confined to exophthalmos of orbital or intracranial tumors. Jackson excluded dural meningioma from his series, not considering it an orbital tumor. Reese's series consists of cases of asymmetric exophthalmos caused by tumors or tumor-like lesions. He excluded proptosis caused by exophthalmic goiter, arteriovenous aneurysm, mucocele, thrombosis of the cavernous sinus, craniostenosis and aneurysm of the ophthalmic artery. In Reese's total of 174 cases of histologically verified tumors are included 21 cases in which the tumors had not caused exophthalmos but were capable of doing so. In the table we have omitted these 21 cases from Reese's series.

Pfeiffer studied 200 consecutive cases of exophthalmos from all causes referred to him for roentgenographic study. Malignant neoplasms occurred in 10 per cent of the total series, being primary in the orbit in 6 per cent, and secondary in 4 per cent. Benign neoplasms and cysts accounted for 25 per cent of his cases. The diagnosis of exophthalmic goiter was made in 6 per cent of the total series. This figure, of course, includes only cases referred for roentgenographic study; thus, the incidence is not comparable to that in our series. In 13 of the 20 undiagnosed cases in Pfeiffer's series, the exophthalmos was of one eye only. Pfeiffer emphasized the value of roentgenography in determining the cause of exophthalmos.

Present Series of Cases.—In 78 (44 per cent) of the 177 cases in our series, the exophthalmos was neoplastic in origin. Malignant neoplasm was present in 38 (21.5 per cent), being primary in the orbit in 19 (10.7 per cent) and secondary in 19 (10.7 per cent). Benign neoplasms occurred in 40 cases (23 per cent). Meningioma, intracranial and intraorbital, represented 20 cases (11.3 per cent), and hemangioma, 12 cases (7 per cent).

Exophthalmos of non-neoplastic origin occurred in 76 cases (43 per cent). In 45 of these 76 cases (25 per cent of the series) the exophthalmos was attributable to exophthalmic goiter. No attempt was made to differentiate exophthalmic goiter into the thyrotoxic and the hyperophthalmopathic type. Arteriovenous aneurysm was responsible for 11 cases (6 per cent) and mucocele for 12 cases (7 per cent).

Classified as undiagnosed were 23 cases (13 per cent). Of these, a diagnosis of orbital tumor was probable in 5 cases, a tumor being palpable in 2 instances.

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42. Dandy, W. E.: Orbital Tumors: Results Following the Transcranial Operative Attack, New York, Oskar Piest, 1941.

43. Jackson, H.: Orbital Tumours, Proc. Roy. Soc. Med. **38**:587-594 (Aug.) 1945.

44. Iles, A. E., and Short, A. R.: Orbital Tumours, Brit. J. Surg. **31**:147-150 (Oct.) 1943.

The mean amount of asymmetry of exophthalmos (chart 2) was found to be of no great assistance in the differential diagnosis of exophthalmic goiter and exophthalmos of neoplastic and other non-neoplastic origin, except to offer a rough indication of what degree of proptosis may be expected with various diagnoses. Thus, a non-neoplastic condition, arteriovenous aneurysm (9.7 mm.), heads the list, while exophthalmic goiter (4.6 mm.) is next to the last in order of frequency.

Diagnosis
Range
Amt. of asymmetry, in mm.
0 2 4 6 8 10
Arterio-venous aneurysm (11) 3-15 9.7
Meningioma (17) 3-19 9.2
Sarcoma, secondary to orbit (6) 5-12 8.5
Sarcoma, primary to orbit (5) 6-10 7.6
Meningioma, optic nerve (3) 6-8 7.0
Inflammatory (6) 7-7 7.0
Hemangioendothelioma (5) 4-12 7.0
Dermoids (4) 4-10 7.0
Malignancy, paranasal sinuses (7) 3-11 6.6
Neoplasm, hematopoetic system (4) 4-13 6.5
Pseudotumor (3) 4-10 6.0
Carcinoma, primary to orbit (6) 3.5-10 6.0
Hemangioma (12) 3-10 5.9
Glioma, optic nerve (3) 3-10 5.7
Mucocele (12) 2.5-12 5.6
Carcinoma, secondary to orbit (4) 5-6 5.5
Exophthalmic goiter (45) 2.5-9 4.6
Osteoma (4) 3-5 3.9

Chart 2.—Mean amount of asymmetry of exophthalmos by cause of exophthalmos. Numbers in parentheses denote number of cases.

Neoplastic and non-neoplastic causes are well mixed between these two extremes.

Chart 3, presenting the distribution of the amount of asymmetry of exophthalmos, and comparing exophthalmic goiter with exophthalmos of neoplastic and other non-neoplastic origins, reveals that a greater degree of asymmetry favors exclusion of exophthalmic goiter from consideration in differential diagnosis of the three types. Specifically, it was

found that of our series of cases of exophthalmic goiter, 58 per cent showed less than 5 mm. of asymmetry, 89 per cent less than 7 mm. and none more than 10.9 mm. This contrasts rather sharply with the figures for the non-neoplastic and neoplastic types, between which there was little difference. In the non-neoplastic group, 26 per cent were found to have less than 5 mm. of asymmetry; 51 per cent, less than 7 mm., and 80 per cent, less than 11 mm. The neoplastic group showed that 24 per cent had less than 5 mm., 54 per cent less than 7 mm. and 90 per cent less than 11 mm.

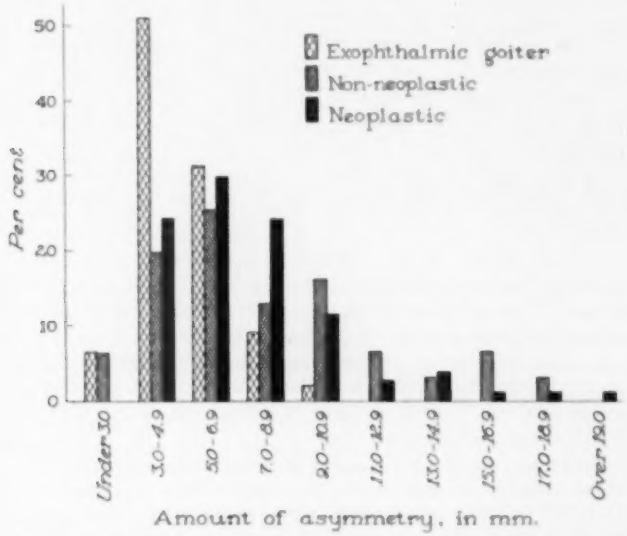

Chart 3.—Distribution of amount of asymmetry of exophthalmos in cases of exophthalmic goiter and of exophthalmos due to neoplastic and to other non-neoplastic causes.

Thus, as pointed out by Rundle and Wilson,[14] a high amount of asymmetry favors the diagnosis of tumor. A low degree of asymmetry, however, does not exclude tumor, since the patient may present himself for diagnosis early because of loss of visual acuity, such as occurs in tumors of the optic nerve. In general, asymmetry of the two eyes of more than 7 mm. is uncommon in exophthalmic goiter and should lead one to favor another diagnosis.

Lastly, the degree of prominence of the less protruding of the two asymmetric eyes was compared for exophthalmic goiter and other causes of exophthalmos. This was done to determine whether the term

"unilateral exophthalmos" as applied to exophthalmic goiter is proper as now employed. We employ the term "base eye" to designate the less prominent of the two eyes.

As previously pointed out, the mean prominence of 200 normal eyes in our control series was 17.3 mm. The mean of measurements for the base eye in all cases in our series, excluding cases of exophthalmic goiter and those of exophthalmos of unknown origin, was 17.2 mm. This compares closely with the normal figure. The mean of measurements for the base eye for the group with exophthalmic goiter, however, was 19.1 mm., a difference of 1.9 mm. This variation was statistically significant and exceeded fivefold the standard deviation of the mean.

Thus, we find that in cases of "unilateral" exophthalmic goiter the supposedly uninvolved eye, that which lies within the normal range of prominence, is more prominent by an average of almost 2 mm. than the eye in cases of exophthalmos of any other cause. Accordingly, since exophthalmic goiter involves both orbits, it is believed preferable to use the term "asymmetric exophthalmos" when discussing cases of exophthalmic goiter in which clinically ocular involvement appears to be unilateral.

SUMMARY

Exophthalmometric measurements (Hertel) of 100 normal subjects fell within a range of 10 to 24 mm., with a mean of 17.3 mm. The maximal normal asymmetry of the eyes was 2.0 mm.

One hundred and seventy-seven cases of asymmetric exophthalmos were reviewed. In 44 per cent of this total the exophthalmos was neoplastic in origin; in 43 per cent, non-neoplastic, and in 13 per cent the cause was not diagnosed.

Sixty per cent of the series fell into six diagnostic categories.

The mean degree of asymmetry of exophthalmos was found to be of no help in the differential diagnosis of the exophthalmos of exophthalmic goiter and that of neoplastic and other non-neoplastic origin.

Asymmetry of the two eyes in excess of 7 mm. is found to be uncommon in exophthalmic goiter.

Data are presented in support of the view that the less prominent of the two eyes is also involved in the exophthalmos of exophthalmic goiter. Thus, although the proptosis may be asymmetric, it is believed to be rarely "unilateral."

A NEW TEST FOR FUNCTION OF THE MACULA LUTEA

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IN A SERIES of articles published between 1844 and 1854, Wilhelm Karl von Haidinger [1] described a phenomenon which became known as Haidinger's brushes *(Haidingersche Lichtpolarisationsbüschel)*. This phenomenon can be seen if polarized light enters the eyes, or if one looks through a Nicol prism at a regular white background or, better still, against the blue sky.

An excellent picture of Haidinger's brushes can be found in Holm's [2] article; this illustration is much better than Helmholtz' reproduction. These brushes consist of two rather bright spots, bordered by two hyperbols belonging together and appearing as bluish on a white background, and of somewhat darker brushes which are yellowish and fill the space between the bluish spots. Rotation of the Nicol prism causes the polarization plane to rotate also.

Haidinger's brushes have evoked the interest of many physiologists and ophthalmologists. Helmholtz,[3] Dimmer,[4] Fortin,[5] Tschermak-Seysenegg [6] and Gording [7] are among the authors who contributed chiefly to the explanation of its mechanism. There is at present no doubt that the phenomenon of Haidinger's brushes is due to the polarization

1. Haidinger, W.: (*a*) Ueber das direkte Erkennen des polarisierten Lichts, Ann. d. Phys. u. Chem. **63**:29, 1844; (*b*) Ueber komplimentäre Farbeneindrücke bei Beobachtung der Lichtpolarisationsbüschel, ibid. **67**:435, 1846; (*c*) Beobachtung der Lichtpolarisationsbüschel in geradlinig polarisiertem Licht, ibid. **68**:73, 1846; (*d*) Beobachtung der Lichtpolarisationsbüschel auf Flächen, welche das Licht in zwei senkrecht aufeinander stehenden Richtungen polarisierten, ibid. **68**:305, 1845; (*e*) Einige neuere Ansichten über die Natur der Polarisationsbüschel, ibid. **96**:314, 1854.

2. Holm, E.: Das gelbe Maculapigment und seine optische Bedeutung, Arch. f. Ophth. **108**:28, 1922.

3. Helmholtz, H. L.: Handbuch der physiologischen Optik, Leopold Voss, Hamburg and Leipzig, 1905, vol. 2, p. 256.

4. Dimmer, F.: Ueber die entoptischen Erscheinungen in der Gegen der Macula lutea, Zentralbl. f. Physiol. **7**:266, 1894.

5. Fortin, E. P.: Nouveau dispositiv pour l'observation entoptique des houppes de Haidinger, Compt. rend. soc. de biol. **63**:103, 1907.

6. von Tschermak-Seysenegg, A.: Einführung in die physiologische Optik, ed. 2, Vienna, Julius Springer, 1947.

7. Gording, E. J.: Lecture given at a meeting of the American Academy of Optometry, Dec. 10, 1949.

power of Henle's layer in the macula lutea. Dimmer [6] demonstrated Henle's layer to have the faculty of dichroism. In an excellent paper, Gording [7] contributed to knowledge of Haidinger's brushes. He proved the correlation of Haidinger's brushes and the macula and demonstrated that Haidinger's brushes are the residue, "and not the result of polarization," thus confirming the statement of Tschermak-Seysenegg.[6]

Cogan [8] stated, however, that "the phenomenon is not exclusively characteristic of the macula . . . that the lens may be responsible for the phenomenon." More will be said later about Cogan's explanation of the production of Haidinger's brushes.

Literature concerning the role of the yellow pigmentation of the macula in its relation to the production of Haidinger's brushes, while interesting, is of minor importance for the purpose of this study.

Great difficulties were experienced in the recognition of Haidinger's brushes as produced by early experimenters, not only by experienced observers but by the average patient as well. The late physiologist Selig Hecht saw Haidinger's brushes for the first time when I asked him to look through a blue filter. He had never been able to perceive them before. To my knowledge, Fortin [6] was the first to make Haidinger's brushes more visible. He used an ultraviolet arc light but was not able to produce the phenomenon for longer than five seconds. (*"Après quatre à cinq secondes si l'on ne déplace pas l'axe du Nicol les louppes s'évanouissent."*) However, he had already pointed out that observation of Haidinger's brushes provided a new method of examination of the macula lutea of the human eye. I did not know of this statement of Fortin's until 1946. It seems that technical difficulties must have prevented Fortin from going further, since I have found no other mention in the literature of the possible value of this sign.

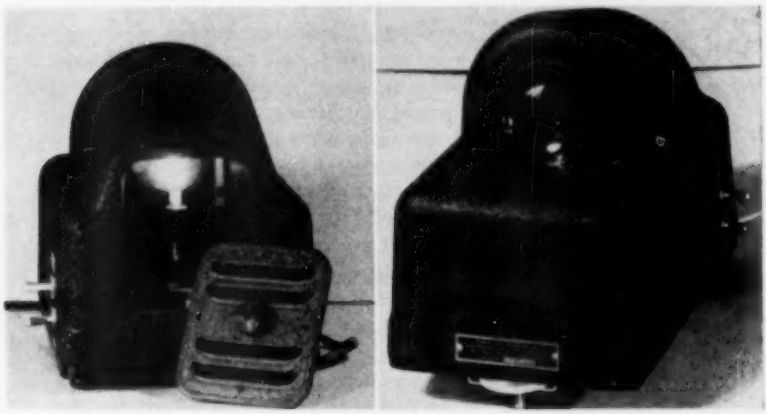
Gehrcke [9] used didymium glass plates 2 cm. thick to produce Haidinger's brushes and to exclude all yellow rays at the same time. In his experiments he reported that 80 to 90 per cent of men over 30 years of age and only 30 per cent under 20 years of age could see the phenomenon, and that 60 to 80 per cent of females of any age could see it. On the contrary, Boehm [10] has shown that with the use of a blue filter ("Lifa" filter G.209; light passage, 430 to 485 micromicrons) 100 per cent of persons examined definitely recognized Haidinger's brushes. In my opinion Gehrcke failed because of the inadequate apparatus with which he worked.

8. Cogan, D. G.: Some Ocular Phenomena Produced with Polarized Light, Arch. Ophth. **25**:391 (March) 1941.

9. Gehrcke, E.: Ueber die Haidingerschen Polarizationsbüschel auf der Macula, Arch. f. Ophth. **120**:567, 1928.

10. Boehm, G.: Ueber maculare Polarizationsbüschel und über einen Polarizationsoptischen Fehler des Auges, Acta ophth. **18**:109, 1940.

To produce an instrument which would give positive results in 100 per cent of normal eyes and which could be used as easily as an ophthalmoscope, the cooperation of the ophthalmologist and the mechanic was necessary. After prolonged experimentation, beginning in 1938, and with the aid of several manufacturers, an instrument was constructed which fills the need (figure).[11] Although the procedure of the test is relatively easy, it would be an error to think that with the primitive improvisation of a filter and a polarization disk the same results could be achieved. In the current model, Haidinger's brushes appear black on a blue background. As the polarization plane of the polarizer rotates with optimum speed, the phenomenon of Haidinger's brushes changes completely. In this respect, Haidinger's brushes can be compared with



Views of the instrument for use in the Haidinger brushes test.

a rotating airplane propeller, a pinwheel or a bundle of hay tied in the middle and rotating around its center.

The question whether Haidinger's brushes were related to the macula lutea (i. e., Henle's layer), the lens, the capsule of the lens or the cornea, or to all four structures, was studied. Cogan stated:

> This experimental production in the lens of a phenomenon [quite like those seen subjectively] which has such striking similarity to Haidinger's brushes suggests that the lens may be responsible for the phenomenon.

This assertion can be disproved easily by the fact that aphakic patients with and without a lens capsule recognize Haidinger's brushes as easily and as readily as persons with intact lenses.

11. This instrument was manufactured for me by the American Measuring Instruments Corporation, 240 West Fortieth Street, New York.

With regard to the role which the cornea may play in the possible production of Haidinger's brushes, Kokott [11a] demonstrated that the central parts of the cornea especially have such an irregular, interwoven anatomic structure that under normal conditions dichroism cannot be expected. Boehm [13] emphasized, too, that the same reason is cause enough for his refusing to accept the cornea as a responsible factor in the production of Haidinger's brushes. Nordenson [12] stated "that the dichroism of the tissue of the cornea cannot be very important, for if so the function of the eyes would be impaired" . . . *(dass die Doppelbrechung der Hornhautsubstanz nicht sehr bedeutend ist, was in Betracht der Leistungsfähigkeit des Auges auch zu erwarten war).* Another proof that Haidinger's brushes may not have any relation to the cornea may be stated as follows: On one's looking only a few degrees eccentrically from the center of the instrument, Haidinger's brushes disappear, because the polarized rays enter an area outside the macula, although the structure in the periphery is more regular than that in the center. My experience has proved that patients with macular defects, i. e., defects in Henle's layer, although possessing almost normal vision and normal cornea and lens, cannot observe Haidinger's brushes. It is logical, therefore, to assume that only the macula lutea is responsible for the production of Haidinger's brushes.

I could never see the peripheral polarization brushes described by Boehm [13] with my instrument. These peripheral polarizing brushes cannot interfere with Haidinger's brushes, as the former can be seen only in patients with dark adaptation, and patients tested by my method are not dark adapted.

After using an instrument which can be manipulated easily and which gives positive results in 100 per cent of persons with a normal macula, i. e., with Henle's layer, and average mental capacity, it was only an additional step to use it in all cases in which a primary or a secondary macular disease was assumed to exist.

An advantage of the test of great importance is that it is independent, to a certain degree, of the acuity of vision. This can easily be verified by holding a lens of +20 D. in front of the normal eye. The change of vision produced in this manner does not alter the easy recognition of Haidinger's brushes. I found that patients with deterioration of sight, not attributable to a macular deficiency, but the result of diseases of other

11a. Kokott, W.: Ueber mechanisch-funktionelle Strukturen des Auges, Arch. f. Ophth. **138**:424, 1938.

12. Nordenson, J. W.: Ueber die Grösse der Doppelbrechung der Horntautsubstanz, Arch. f. Ophth. **105**:721, 1921.

13. Boehm, G.: Ueber ein neues entoptisches Phänomen im polarizierten Licht: "Periphere" Polarizationsbüschel, Acta ophth. **18**:143, 1940.

parts of the eyeball, can see Haidinger's brushes if the visual acuity is not less than 20/200 or, in a few cases, not less than 20/400.

To control the patient more satisfactorily, the direction of the rotation of Haidinger's brushes can be changed, so that the patient can see the brushes rotating either clockwise or counterclockwise. This can be accomplished by placing a cellophane® sheet in front of the bulb of the instrument. In special cases I have found it practicable to place a prism of 10 degrees, base up or base down, in front of either eye to produce double vision. A piece of cellophane® is placed in front of each eye at the same time, and in this way the patient can observe simultaneously, with the two eyes, Haidinger's brushes rotating clockwise and counterclockwise. Cogan [8] was the first to note the effect of the cellophane® on the rotation of Haidinger's brushes. The explanation for this occurrence, given by Gording,[7] is self explanatory, and I accept it readily. Gording proved that by using the cellophane,® as previously indicated, the plane of polarization was reversed by 90 degrees and the stroboscopic effect, as he defined the propeller-like phenomenon, appeared when the rotation of the polarizer was counterclockwise, if it had been clockwise before.

Results of the clinical application of Haidinger's brushes as a test of function of the macula lutea are summarized.

I. Congenital abnormalities of the anatomic structure of the macula lutea.

1. A brother and sister, both albinos, did not recognize Haidinger's brushes.

2. In cases of unilateral convergent strabismus and amblyopia, one must distinguish between (*a*) those in which Haidinger's brushes were seen from the beginning and visual acuity improved after two months of occlusion, and (*b*) those in which Haidinger's brushes were not recognized from the start and no improvement of visual acuity was noted after two months of occlusion. In this way, it is possible to predict whether occlusion or exercises (which I never employ) will be of value to persons with strabismus and amblyopia.

3. I had no occasion to examine patients with complete color blindness (achromatopsia), but Boehm [10] found that Haidinger's brushes were not seen by these patients.

4. A pair of twins with hereditary familial degeneration of the macula were examined; they did not recognize Haidinger's brushes.

II. Primary acquired lesions of the macula lutea.

1. All cases included in the category of edema of the retina, especially of the macula lutea, are to be mentioned. Duke-Elder [14] wrote: "The

14. Duke-Elder, W. S.: Text-Book of Ophthalmology, Diseases of the Inner Eye, St. Louis, C. V. Mosby Company, vol. 3, p. 2591, 1941.

clinical picture of retinal oedema in its milder aspects is frequently difficult to detect." It is my opinion that use of the Haidinger brushes test of the function of the macula lutea makes possible the detection of such a condition with great accuracy and rapidity. Edema of the macula is almost always unilateral; I, personally, have never seen a case of bilateral edema. This test makes comparison of the involved eye and the normal eye relatively easy and reliable.

I have been able, by the use of the new test, to diagnose typical chorioretinitis centralis serosa (Kitahara) relatively often in cases in which the condition had previously been overlooked.

The prognosis of lesions of the macula depends often on the early recognition of the process, early exploration of the cause and causal or palliative treatment. Therefore early macular testing is, without question, of great importance. To the primary acquired lesions of the macula belong all conditions which Duke-Elder summarized under the heading of central angiospastic retinopathy, for example, the central recurrent retinitis of Fuchs [15] and Baillart's [16] capillaritis. From the frequency with which these ailments appear in modern ophthalmologic literature, the need for a test such as this is impressive.

2. Senile degeneration of the macula in its various aspects is easily diagnosed with the new test, even in cases in which the ophthalmoscopic examination was to some degree impossible, owing to changes in the lens or in the vitreous or in both. One case may be mentioned in which the pathologic changes in the macula as seen with the ophthalmoscope were so minute that an incorrect diagnosis of retrobulbar neuritis was made. The future course of the disease confirmed the diagnosis readily made with the new test. In this connection may be discussed the problem of whether it is possible to make the differential diagnosis of acquired macular disease and lesions of the optic nerve with the new test. It has been established that Haidinger's brushes are seen in cases of optic nerve atrophy in which central vision was not less than 20/60. A case may illustrate this: A patient with unilateral glaucomatous atrophy of the optic nerve (tension 72 mm. of mercury, Schiøtz; concentric constriction of the visual field) saw Haidinger's brushes with the affected eye. But persons with atrophy of the optic nerve and with vision of 20/200 or less did not recognize Haidinger's brushes. This contradiction may be explained by the fact that in cases of optic nerve disease in which Haidinger's brushes are not recognized the papillomacular bundle is involved, or there is a secondary degeneration of Henle's layer or both.

15. Fuchs, E.: Ein Fall zentraler rezidivierender syphilitischer Netzhautentzündung, Zentralbl. f. prak. Augenh. **40**:105, 1916.

16. Baillart, P.: Capillarites et lésions lacunaires de la rétine, Ann. d'ocul. **171**:97, 1934; L'oedème de la rétine, ibid. **175**:133, 1938.

The participation of the macula in optic nerve disease has recently been described by Fischer.[17] He found participation of the macula in about 7 per cent of 180 patients with retrobulbar neuritis.

3. In many cases of healed lesions of the anterior part of the eyeball, the remaining opacities and other residues of the ailment do not explain the deterioration of vision. I mention, among others in this category, a case of iridocyclitis tuberculosa of long duration, with final vision of 20/100, in which examination of the macula, owing to numerous posterior synechias, was impossible but in which the optic nerve did not show atrophy. In this case the Haidinger brushes test gave negative results, making it almost certain that the macula lutea had undergone pathologic changes. Fuchs,[18] in his anatomic studies of participation of the macula lutea in diseases of the eye, found that macular degeneration may be present in cases of contusion, perforation, suppurative keratitis, endogenous inflammation of the anterior parts, pressure on the eyeball from behind and high intraocular pressure. He emphasized that a pathologic condition of the macula can remain without visible changes in the fundus even with ophthalmoscopic examination. It is evident that with the Haidinger brushes test it is almost impossible to overlook such an unexpected involvement of the macula.

Use of the Haidinger brushes test will certainly be extended, and it will be of value in the early diagnosis of various diseases of the eyeball in which the macula lutea, i. e., Henle's layer, is involved. The test will make possible differential diagnosis of diseases of the macula and of the optic nerve. But the most important factor of this new "old" test is the early and easy detection of macular involvement.

SUMMARY

1. Haidinger's brushes is a phenomenon due to the dichroism of the macula lutea of the retina, particularly of Henle's layer.

2. Haidinger's brushes can be recognized by persons with normal eyes in 100 per cent of cases, regardless of age and sex.

3. All kinds of ocular anomalies and diseases of the eye in which there is participation of the macula lutea, especially Henle's layer, can be detected in the very early stages of the disease.

17. Fischer, Franz: Makulaveränderungen bei akuter retrobulbärer Neuritis, Klin. Monatsbl. f. Augenh. **114**:511, 1949.

18. Fuchs, E.: Ueber Beteiligung der Macula lutea an Erkrankungen des Auges, Arch. f. Ophth. **97**:57, 1918.

TORSION OF THE EYE ON OBLIQUE GAZE

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WHETHER or not torsion of the eye occurs on oblique gaze has been a subject of controversy for some time. Some have held for instance, that, on upward and outward gaze the eye intorts [1]; some, that it extorts,[2] and some, that it does neither.[3] The group who have claimed that torsion occurs are divided into those who speak of true torsion and those who say that only apparent (false) torsion exists.

The methods used for determining the amount of torsion have been based on the study of after-images and models, mathematical analysis and speculation. It seems that the question is subject to direct experimental approach.

It is difficult to estimate torsional movements unless one observes in the vertical plane containing the visual axis of the eye under investigation (fig. 1).

PRESENT INVESTIGATION

Method.—After instillation anesthesia, and while the subject gazes ahead, ink marks are made at the upper and the lower limbus to identify the vertical meridian of the cornea. The subject then gazes into the observer's eye. A small plumb line is adjusted so as to bisect the subject's pupil. As the direction of gaze is shifted laterally or medially, the plumb line is shifted also. The ink marks are observed with reference to the plumb line.

Results.—On upward and outward gaze and on downward and inward gaze the eye extorts. In the other two oblique positions it intorts (fig. 2).

COMMENT

The differentiation between "true" and "false" torsion seems to me to be only verbal. It appears fair to say that when the 6 to 12 o'clock meridian of the eye is no longer vertical the eye has torted, no matter by what mechanism this has occurred.

1. Chevasse, B.: Worth's Squint, ed. 7, Philadelphia, The Blakiston Company, 1939, pp. 327 and 356.

2. Le Conte, J.: Sight, New York, D. Appleton-Century Company, Inc., 1881, p. 194.

3. (*a*) Savage, G. C.: Physiology and Pathology of the Ocular Muscles, in The American Encyclopedia and Dictionary of Ophthalmology, Chicago, Cleveland Press, 1917, p. 7900. (*b*) Marquez, M.: Supposed Torsion of the Eye Around the Visual Axis in Oblique Directions of Gaze, Arch. Ophth. **41**:704 (June) 1949.

Maddox [4] calculated the amount of torsion which should occur on the basis of Listing's law, as shown in the following tabulation:

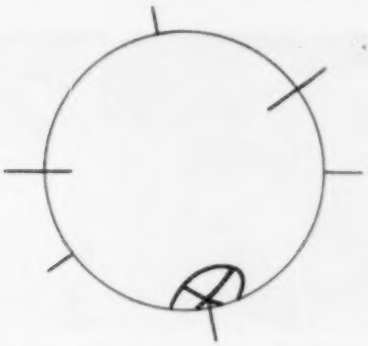

Fig. 1.—Model eye seen from above and to the right, showing difficulty in estimating vertical corneal meridian.

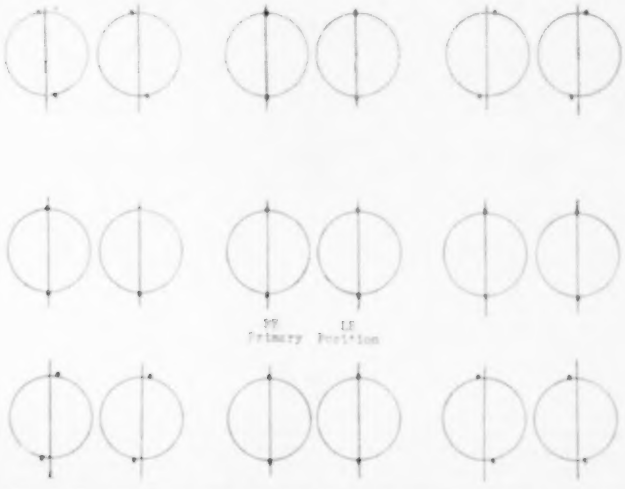

Fig. 2.—Torsion of eyes in various positions as observed along the visual axis.

The amounts of torsion I observed were of the order of magnitude predicted by Maddox. It should be noted that the torsion increases in

4. Maddox, E. E., cited by Savage,[5a] p. 7901.

an exponential manner as the gaze shifts obliquely from the primary position. Up to an angle of 20 degrees there is less than 2 degrees of torsion. This is indeed a small amount.

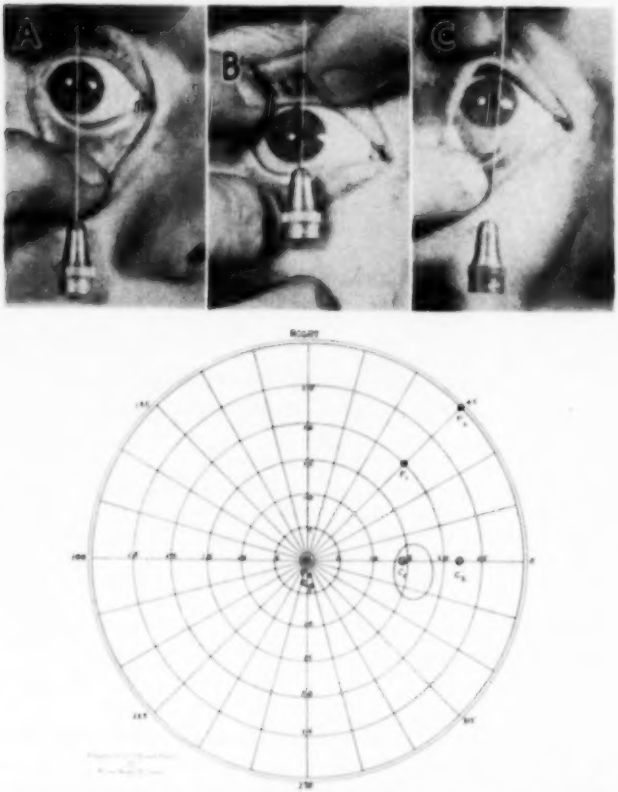

Fig. 3.—Below is the tangent screen as seen by the subject. F_0, F_1 and F_2 are fixation points; C_0, C_1 and C_2 are corresponding positions of the camera. Above are photographs of the eye in the various positions of fixation. *A* (F_0C_0), 0 degrees of torsion, with the gaze straight and ahead; *B* (F_1C_1), 20 degrees up and out, with about 2 degrees of extorsion; *C* (F_2C_2), 30 degrees up and out, with about 5 degrees of extorsion.

Sherrington[5] proposed that the torsional movements were in the direction opposite the apparent movements of after-images, since the

5. Sherrington, C. S., cited by Chevasse,[1] p. 356.

retinal image is inverted. This is not so. Torsion is correctly represented by the tilting of the after-image. Distortions of the after-images by perspective effects have been correctly explained by Le Conte,[5] Marquez [5b] and others.

Rotation About an Axis 45 Degrees from the Horizontal

Rotation, Degrees ...	5	10	15	20	25	30	35	40	45
Torsion	6½′	26′	1°	1° 47′	2° 49′	4° 6′	5° 40′	7° 33′	9° 44′

CONCLUSIONS

In oblique positions of gaze the sagittal meridian of the eye is not vertical. On up and out and down and in gaze this meridian is extorted. In the other two oblique directions it is intorted.

The amount of torsion is of the order of magnitude predicted by Maddox on the basis of Listing's law.

After-images tort in the same sense as the torsion of the eye itself.

Lakeland Clinic.

Clinical Notes

GLIOMA OF THE RETINA IN FATHER AND CHILD

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In January 1927 at Kansas City, Kan., a 2 year old white boy had his left eye removed because of a glioma of the retina, verified pathologically. There was no extension into the optic nerve. The boy grew up and married, and in February 1948 his wife gave birth to a girl. In August 1948, when the child was 6 months old, the parents noticed that her right eye was larger than her left.

The first ophthalmic examination was at the Manhattan Eye, Ear and Throat Hospital on October 26, at which time the right eye was noted to be rather large, the cornea steamy, the iris discolored, the tension extremely high as determined by palpation, and the globe injected. Examination the same day, with the patient under ether anesthesia and with the left pupil dilated, showed almost complete detachment of the retina of the left eye, with yellowish white masses and new-formed blood vessels. The right eye was enucleated the same day, October 26. Roentgenograms of the left eye with the detached retina did not reveal calcium deposits. Roentgenologic examinations of the skull, sternum and chest showed no metastases.

Section of the optic nerve of the enucleated right eye showed no glioma tissue. A paraffin section of the right eye on November 4, one week after the first examination, revealed a massive glioma with many rosettes and some areas of calcification (figs. 1 and 2). Since the presence of rosettes indicates a lower degree of malignancy and there was no extension into the excised optic nerve, roentgen therapy to the left eye was started on November 5. At this time almost all the retina visible with the ophthalmoscope was involved by the glioma. Because the child had diarrhea, vomiting and a rise in temperature, radiation was not given again until November 15, a lapse of ten days. The roentgen therapist was requested to ignore the possibility of producing a radiation cataract in administering the radiation.

On December 9, the upper part of the gliomatous mass in the left eye had already receded to some degree. On December 22 the child went home for Christmas and returned December 29 for more radiation. At this time most of the upper portion of the retina was clear of tumor, and many pigment flecks were present in the retina in this area. In the periphery below the same picture was beginning to develop. The media remained clear. By March 16, 1949 the mass had shrunk to about four times the size of the optic disk, and most of it was in the temporal portion of the retina. There were more pigment flecks in the retina, which had become free of the tumor, and a few small areas of retinal atrophy were appearing for the first time. Roentgenologic examination for metastases

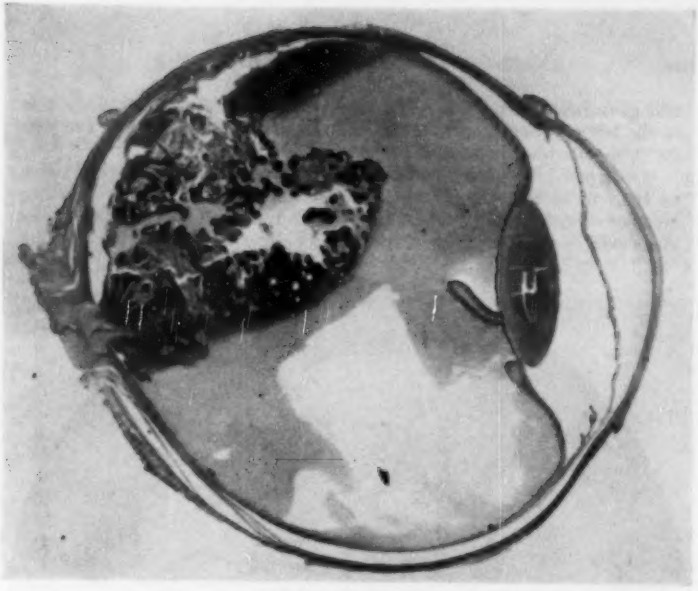

Fig. 1.—Section of right eye, with glioma of the retina.

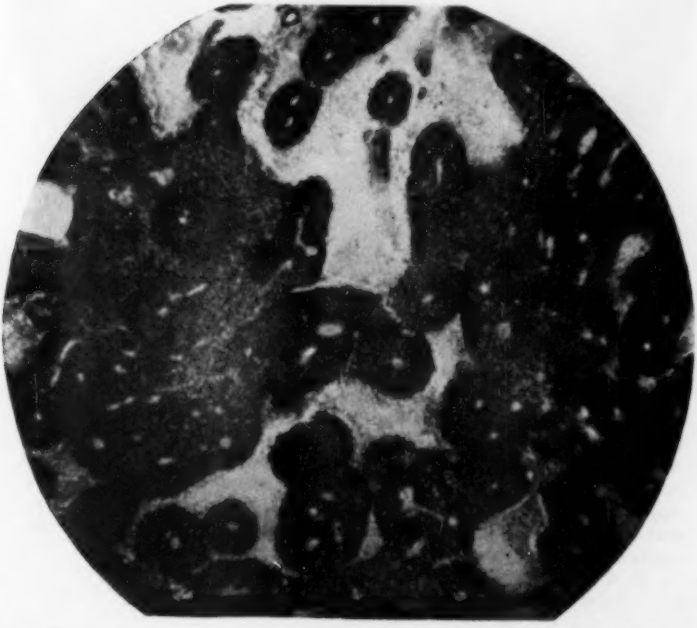

Fig. 2.—Rosette formation and areas of calcification in a glioma of the retina (right eye).

still gave negative results. The left eyebrow and the lashes of the lids of the left eye were gone, and the skin in the region of the left eye was red and somewhat edematous.

On April 17 the mass had begun to grow again and was about twice as large as at the last examination, on March 16. There were more areas of retinal atrophy, with an increase in the amount of pigment flecks and some yellowish areas, which were interpreted as calcifications

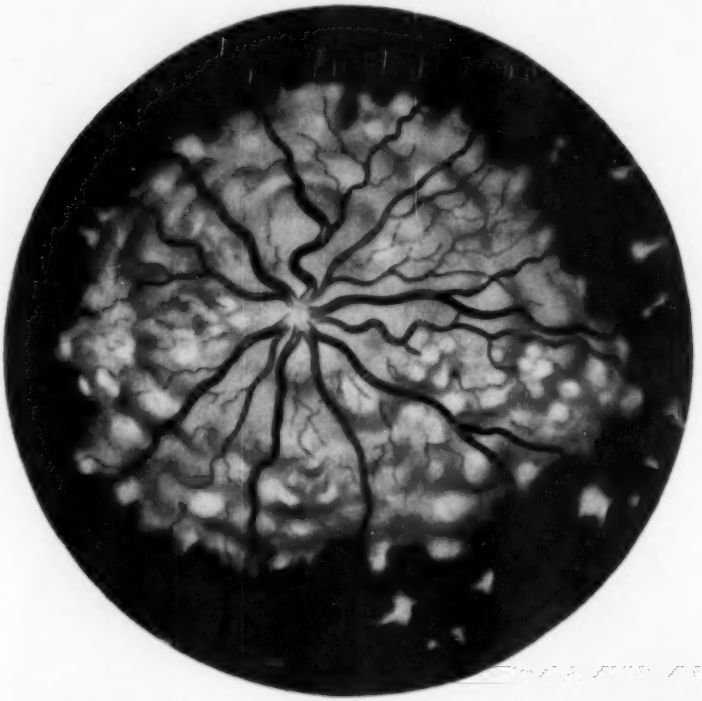

Fig. 3.—Glioma in the left eye, with areas of retinal atrophy, flecks of pigment and yellowish areas, suggesting calcifications.

(fig. 3). The parents, on being consulted, decided that since the hospital staff could not be sure that there would be no extension into the optic nerve, even though it was planned to give more radiation over the lateral field, they would rather have the eye enucleated than run the risk of having the child die. They feared that with roentgen therapy they were endangering their child's chance to live; at the same time, they had no real assurance that she would be cured and retain useful vision. Accordingly, the eye was enucleated.

Examination of the excised optic nerve showed no extension of the glioma into the nerve tissue. The enucleated globe, likewise, showed no involvement of the optic nerve, and the tumor was limited to the retina immediately surrounding the optic nerve, but with more on the temporal than on the nasal side (fig. 4). The glioma in this eye also had rosettes and some calcium deposits (fig. 5). The pigment flecks noted with the ophthalmoscope were in the retina proper, to which they were migrating from the pigment epithelium layer. The rods and cones

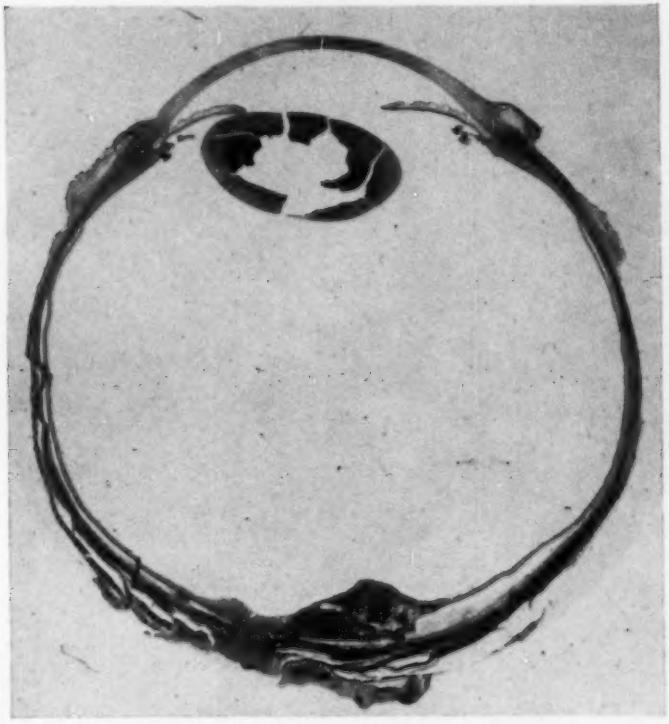

Fig. 4.—Section of left eye, with glioma of the retina.

were rather atrophic, but the nuclei of the rods and cones still stained well and had not migrated. The macular area could not be differentiated because it was completely involved by the glioma cells.

The total radiation given was as follows:

The anterior field, 3 cm. in diameter, received a total of 3,500 r in air, and the lateral field, 3 by 2.5 cm. in diameter, received 3,200 r in air, the radiation factors being 200 kilovolts, 19 milliamperes, 0.5 mm. copper and 1 mm. aluminum of filtration and a target skin distance of 50 cm. Both fields were treated daily, 300 r being divided between them. The

estimated tumor dose was 5,300 r; it was considered that the most effective irradiation came through the direct anterior portal.

The amount of radiation therapy to which this child's eye was exposed was sufficient to destroy a great deal of glioma tissue, but it was also sufficient to cause damage not only to the adnexa but also to the cornea and the lens. I am certain that if the eye had not been enucleated all the complications and sequelae of excessive irradiation would gradually

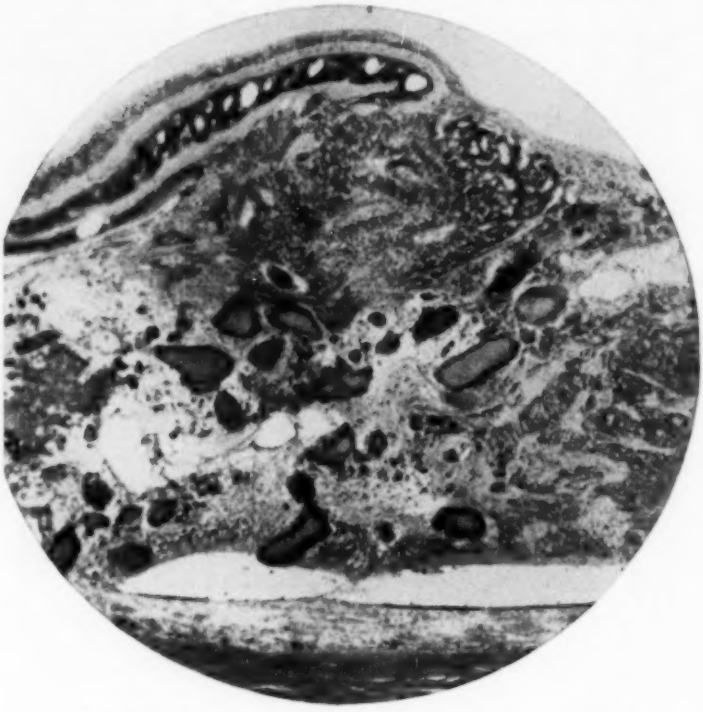

Fig. 5.—Rosette formation and deposits of calcium in glioma (left eye).

have developed and the eye would have had no vision. It seems, therefore, that radiation therapy for glioma of the retina should not be undertaken if more than one sixth, or one fourth, at the most of the retina is involved by glioma.

Reese [1] stated that he had in his series "of 184 cases of retinoblastoma only 5 survivors with children. The children total 8, and 7 of these had

1. Reese, A. B.: Heredity and Retinoblastoma, Arch. Ophth. **42**:119-122 (Aug.) 1949.

bilateral retinoblastoma. These figures are sufficiently impressive to me to interdict the bearing of progency by all survivors of retinoblastoma." He further concluded that "there is no contraindication to healthy parents who have had one child with retinoblastoma having more children. A survivor of retinoblastoma should not have children."

The case here reported is further evidence in support of Reese's statements.

CONCLUSIONS

1. Radiation therapy of a glioma of the retina should not be attempted if more than one sixth, or at the most one fourth, of the retina is involved. If only one eye is affected and the other eye is normal, radiation therapy should not be given, regardless of how small an area is involved; the eye should be enucleated.

2. All survivors of glioma should be warned not to have children.

Annual Reviews

STRABISMUS

Review of the Literature

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THIS REVIEW, written at the request of the editor, is restricted to the topic of concomitant strabismus. Its aim is a survey of the pertinent literature on this subject published in 1949 and in the first quarter of 1950. A complete coverage of the literature available to the reviewer has been attempted; what may have been overlooked or been unavailable will be added in a review planned for next year.

ETIOLOGY; CLASSIFICATION

In spite of the enormous effort expended by some of the best minds in ophthalmology, the riddle of the etiology of strabismus is still not solved to everyone's satisfaction. The problem is taken up again by Piper [1] in a publication which is technically outside the scope of this review, since it was published in December 1948, but which is sufficiently significant to warrant its inclusion here.

Piper attempts to explain all forms of nonparalytic strabismus—manifest as well as latent—from a single point of view. His exhaustive paper, which is not easy to read, may be summarized as follows:

Piper rejects all etiologic explanations which seek the primary cause of strabismus in the periphery, and in this category he includes not only anatomic anomalies but also refractive errors and sensory disturbances. In his opinion, the primary cause of nonparalytic strabismus is always an imbalance in the central nervous arrangement for ocular movements. The cortical fields, which normally control the relative position and the movements of the two eyes (the binoculus), are weakened; subcortical centers, which govern functions of the single eye, are disinhibited and gain control of the relative position of the eyes. In the case of horizontal strabismus the convergence function represents the controlling mechanism for binocular function. It may give way to a subcortical accommodative controlling mechanism, and this leads to a convergent strabismus if excessive impulses are required (hypermetropia) or to a divergent strabismus. The primary thing is the central change of command. In vertical deviations the cortical centers active in the waking state lose control to the subcortical centers normally active in sleep (Bell's phenomenon).

1. Piper, H. F.: Die Schielkrankheit, Arch. f. Ophth. **148**:555, 1948.

The primary strabismus is purely dynamic, i. e., solely determined by the imbalance between the cortical and the subcortical impulses; it is characterized by a great instability of the condition; in the case of vertical strabismus it is represented by an alternating hyperphoria. In the course of development the deviation (manifest or latent) becomes concomitant, and in the final stage secondary changes lead to anatomic fixation of the angle of squint and to sensory changes, such as suppression, amblyopia and anomalous correspondence.

Sensory processes ("fusion tendency") cannot compensate for primary anomalies of the relative position of the eyes. Rather one must assume that if the binocular motor function ("convergence position," "waking position") is good, then the optomotor reflexes are active (result orthophoria or heterophoria). If the subcortical impulses dominate, the optomotor reflexes are insufficiently effective or not at all (heterotropia). Whether or not the optomotor reflexes are active can be determined by measuring the minimum time required to regain single vision after excluding one eye from fixation. This Piper has done by means of an experimental arrangement making use of an episcotister disk.

It is tempting, but quite impossible, to discuss Piper's contribution in detail, but certain points must be briefly made. Piper's theory suffers from the difficulty encountered by all theories which assume a supranuclear origin of concomitant strabismus; that is, it is not possible to show how primary changes in supranuclear functions, which must affect both eyes, can influence the relative position of the eyes. Piper tries to circumvent this by assuming that the command is taken over by subcortical centers which influence the position of each eye separately. In so doing, he starts from assumptions for which there is neither physiologic nor anatomic evidence. There is no evidence that supranuclear centers govern the movement of the single eye or that they are autonomous. Furthermore, there is no evidence whatever that concomitant hyperphorias develop from dissociated, alternating hyperphorias. It always remains necessary to assume the presence of "peripheral" and "sensory" embarrassments. Their presence is demonstrable. Why insist in all cases on calling them secondary to hypothetic primary imbalances of the motor innervation? Why not admit, rather, an imbalance between the sensory and the motor impulses, which normally make for the harmonious sensory-motor cooperation of the binoculus?

This conclusion would imply that multiple factors are primarily responsible for the development of heterophorias and heterotropias. This is admitted by Comberg,[2] who distinguishes fundamental factors, precipitating factors and factors leading to the establishment of the

2. Comberg, W.: Verhältnisse bei der Entstehung des Begleitschielens, Arch. f. Ophth. **149**:562, 1949.

condition. Among the fundamental factors Comberg lists faulty development in the binocular visual act, pointing out, however, as does Abraham,[3] that fusion is not "congenitally" weak but, rather, "normally" weak in early life. Comberg emphasizes especially the importance of the nearness factor, which reduces the size of the binocular field in infants, and the significance of the physiologic weakness of their peripheral field, their functional "tubular" field. Other fundamental factors are refractive differences between the two eyes, imbalances between accommodation and convergence and anomalies of the "position of rest." The precipitating factors are those which cause a failure of fusion either with increasing use of the eyes in close work or after a disorder affecting one eye or a general disease. The development of suppression, amblyopia, anomalous retinal correspondence and secondary muscular changes, finally, leads to a more or less fixed concomitant motor anomaly.

An interesting attempt to explain the overaction of an inferior oblique muscle on an innervational basis was made by Guibor,[4] who rejected peripheral causes in the genesis of this condition, just as did Piper [1] and Meesmann.[5] Guibor found that in some cases the cure of a horizontal deviation by nonsurgical means (atropinization, use of glasses, occlusion or incorporation of prisms) made an overfunction of the inferior oblique disappear. He concluded that excessive accommodative or convergence impulses irradiated to the nucleus of the inferior oblique muscle, causing what he termed a synkinetic overfunction of that muscle.

It is not clear why this irradiation should be selective, nor is it evident from the case histories whether the overfunction actually disappeared or whether only the hypertropia in the primary position was overcome. Moreover, a synkinetic genesis certainly cannot apply to all cases of overaction of the inferior oblique muscle. Nevertheless, Guibor's observations are worth further study and attention.

DIAGNOSIS AND SYMPTOMATOLOGY

Among the tests most widely used for determination of the relative position of the eyes are those which require observation of the movements of redress of the patient's eyes. It is of great practical interest to know the accuracy with which these movements can be observed. Ludvigh [6] has made a valuable contribution to the solution of the question

3. Abraham, S. V.: A New Classification of Nonparalytic Strabismus, Am. J. Ophth. **32**:93 (Jan.) 1949.

4. Guibor, G. P.: Synkinetic Overaction of the Inferior Oblique Muscle, Am. J. Ophth. **32**:221 (Feb.) 1949.

5. Meesmann, A.: Weitere Beiträge zur operativen Behandlung des nichtparetischen Hohenschielens, Arch. f. Ophth. **149**:503, 1949.

6. Ludvigh, E.: Amount of Eye Movement Objectively Perceptible to the Unaided Eye, Am. J. Ophth. **32**:649 (May) 1949.

of the minimum amount of eye movement preceptible to the unaided eye. He concluded that under ideal conditions excursions of less than 1 to 2 Δ cannot be reliably perceived. [Knowing how much less ideal the conditions of examination ordinarily are, I would suggest that the lower limit to be counted on clinically should be set at 3 to 4 Δ.]

The monocular and binocular fields of vision in patients with concomitant strabismus were studied by Casari.[7] In general, he found paracentral rather than central scotomas; these scotomas tended to be larger in binocular tests, and in cases of alternating strabismus they were present only on binocular examination. In some cases the scotomas became smaller or disappeared after successful treatment.

Miles [8] studied the flicker fusion frequency in 44 patients with amblyopia ex anopsia. He could confirm the older findings of Lohmann and Teräskeli that the flicker fusion frequency in the central area of amblyopic eyes is increased, approaching that of the periphery and suggesting a suppression of central cones.

Meesmann [5] states the belief that the absence of torsional deviations, and consequently the absence of a head tilt, is an important sign in the differential diagnosis of primary overfunction of an inferior oblique muscle and secondary overfunction due to paresis of an ipsilateral superior oblique muscle. According to Meesmann, this is explained by the fact that in primary overfunction the inferior oblique muscle is overactive mainly in the adducted position of the eye, in which this muscle is primarily an elevator, whereas there is overfunction of the inferior oblique muscle in its entire field of action when the antagonistic superior oblique muscle is paretic.

NONSURGICAL TREATMENT; ORTHOPTICS

The most original paper concerned with the nonsurgical treatment of strabismus published during the past year is that by Abraham,[9] who suggests the use of miotics, mainly pilocarpine, in the treatment of concomitant esotropia of accommodative origin. Abraham's idea behind this therapy is that pilocarpine should produce a spasm of accommodation of peripheral origin, thus obviating the need for a central accommodative impulse, which is accompanied with a corresponding convergence impulse. According to Abraham, this type of therapy has resulted in cure in a number of cases, "cure" meaning a parallel position of the eyes without the use of corrective glasses, the effect lasting for months.

7. Casari, G.: Reperti scotometrici nello strabismo dinamico, Rassegna ital. d'ottal. **18**:338 (Sept.-Oct.) 1949.

8. Miles, P. W.: Flicker Fusion Frequency in Amblyopia ex Anopsia, Am. J. Ophth. **32**: (pt. 2):225 (June) 1949.

9. Abraham, S. V.: The Use of Miotics in the Treatment of Convergent Strabismus and Anisometropia, Am. J. Ophth. **32**:233 (Feb.) 1949.

[Without personal experience to support a criticism of Abraham's work, I would, nevertheless, point out that it is not understandable how the effect of the pilocarpine can be a lasting one, once the use of the drug is stopped, unless it somehow teaches the hypermetropic child the trick of how to dissociate accommodation from convergence, or unless the proper use of the eyes during the time the drug is being given helps the patient to build up fusion to the point where he becomes heterophoric rather than heterotropic. It must also be considered that the effect of pilocarpine in normal eyes is rather erratic and that it by no means invariably produces a spasm of accommodation (Fanta [10]). Nevertheless, judging from the results obtained by Abraham, the effect of pilocarpine both on the eyes of children and on the relative position of the eyes of patients with strabismus appears to be worthy of further study.]

A worth while contribution to the general subject of orthoptics has been made by Miss Julia Lancaster.[11] Her discussion of the basis, aims and limitations of this field should be read in full by any one who wishes to form a picture of what orthoptic training can and cannot be expected to achieve and of how this achievement is reached. A few salient points will be noted here.

Binocular vision is made up fundamentally of two parts. One is innate, structural, uninfluenced by experience and training; the other consists of acquired binocular skills. Orthoptics is concerned with the second part; it cannot alter the first, but can only assist the patient in acquiring the best binocular skills of which his eyes are capable. Orthoptics thus becomes a teaching process, subject to the laws of learning and teaching; a good orthoptist is a good teacher. The five steps of learning—attention, awareness, response, satisfaction, repetition—apply also to orthoptic training. Properly selected stimuli will make the correct response easy for the patient and give him the satisfaction necessary for repetition. Orthoptic therapy is thus an opportunity offered the patient rather than a treatment.

This sound approach to the basis of orthoptics should go a long way toward dispelling misunderstandings which still becloud this field of therapy.

A study of the horizontal fusional amplitudes in relation to age and with the use of two instruments (a variable prism stereoscope and the synoptophore) and two types of targets (fusion target; stereoscopic target) was made by Mellick.[12] He observed no significant influence of age on the fusional amplitudes but found the amplitude of convergence to be

10. Fanta, H.: Die Wirkungsweise des Pilokarpin bei normalen Augen, Ophthalmologica **115**:338, 1948.

11. Lancaster, J. E.: The Learning Process in Orthoptics, Am. J. Ophth. **32**:1577 (Nov.) 1949.

12. Mellick, A.: Convergence: An Investigation into the Normal Standards of Age Groups, Brit. J. Ophth. **33**:775 (Dec.) 1949.

twice as large for distance and near vision on the synoptophore as with the prism stereoscope. His average figures for 561 subjects, of all ages, are presented in the accompanying table. The amplitudes found by Mellick agree on the whole with those reported by Tait.[13]

Mellick [14] has also reported on the result of orthoptic treatment of patients with convergence insufficiency seen during one year. He divided his 63 patients into neurotic (48) and non-neurotic (15) subjects. The results in the two groups were not appreciably different, and the cure of symptoms was always accompanied with improvement in the objective signs. Nevertheless, Mellick feels that convergence insufficiency is a psychosomatic disorder, more especially since he saw during the same period 18 patients with convergence insufficiency but no symptoms and 29 patients with subjective symptoms of convergence insufficiency but without objective signs.

Average Values for Amplitudes of Concergence and Divergence in 561 Normal Subjects

	Variable Prism Stereoscope		Synoptophore	
	Fusion Target	Stereoscopic Target	Fusion Target	Stereoscopic Target
	Amplitude of Convergence			
Distance	17.66 ± 0.26 △	18.20 ± 0.50 △	38.47 ± 0.76 △	40.33 ± 0.79 △
Near	26.42 ± 0.39 △	22.16 ± 0.56 △	51.36 ± 0.83 △	55.08 ± 0.86 △
	Amplitude of Divergence			
Distance	7.97 ± 0.10 △	9.09 ± 0.15 △	10.78 ± 0.12 △	11.77 ± 0.16 △
Near	13.61 ± 0.16 △	12.04 ± 0.15 △	12.63 ± 0.12 △	13.36 ± 0.16 △

[I always feel a little uneasy when subjective ocular symptoms are attributed to a psychoneurotic constitution in the presence of valid objective signs. Many patients with convergence insufficiency do indeed exaggerate their symptoms, and it is not always possible to be sure that the convergence insufficiency is the real cause of their trouble. But there is also no doubt that the higher degrees of exophoria and convergence insufficiency place on the patient a tremendous, unending strain, which may well lead to psychoneurotic symptoms in less stable persons. An early cure of the ocular condition would have made much happier people of these patients. Incidentally, Mellick does not say how the psychoneurotic patients were differentiated from the non-neurotic patients—certainly not a simple task.]

The handling of the amblyopic patient is discussed by Wheeler,[15] who places justified emphasis on the differentiation of true amblyopia

13. Tait, E. F.: Fusional Vergence, Am. J. Ophth. **32**:1223 (Sept.) 1949.

14. Mellick, A.: Convergence Deficiency: An Investigation into the Result of Treatment, Brit. J. Ophth. **34**:41 (Jan.) 1950.

15. Wheeler, M. C.: The Handling of the Amblyopic Patient, Am. J. Ophth. **32**:1261 (Sept.) 1949.

ex anopsia and a "pathologic amblyopia" without ophthalmoscopically visible signs. If the visual acuity does not show a trend toward improvement within a reasonable time, one should give the child the benefit of the doubt and not insist on torturing him with occlusion.

Feldman [16] reports continued good results in treatment of amblyopia with his telescopic amblyoscope, and Winkelman [17] describes briefly a new projection tachistoscope, which should prove very useful in clinical studies and orthoptic treatment.

SURGICAL TREATMENT

A relatively large number of papers has appeared during the past fifteen months dealing with the surgical treatment of ocular deviations. From all these papers there is evident an interesting trend toward a more physiologic approach to the indications for and technic in the surgical treatment of extraocular muscles. Thus, it is now quite generally admitted that it is impossible to make hard and fast rules as to the exact amount of correction,[18] solely on the basis of the angle of deviation. Also, the behavior of convergence and divergence is no longer considered the all-important factor in the choice of operation.

Lee and O'Brien,[18b] for instance, emphasized that it was not necessary to distinguish in cases of concomitant exotropia between divergence excess and convergence insufficiency in determining the type of operation. These authors also stated that they found no influence of the state of the retinal correspondence on the final operative result, an experience which I fully share.

In general, however, Lee and O'Brien noted that similar amounts of recession resulted in greater changes in the position of the eyes if the preoperative angle was large rather than if it was small; Scobee [19] and Burian [18d] concurred in this statement.

Scobee [18c] was particularly emphatic about the difficulties of predicting the result of operations on extraocular muscles in terms of degrees of correction per millimeter of change in the position of the insertion

16. Feldman, J. B.: Further Studies in Amblyopia, Am. J. Ophth. **32**:1394 (Oct.) 1949.

17. Winkelman, J. E.: Projection Tachystoscope for Orthoptic Treatments, Am. J. Ophth. **33**:461 (March) 1950.

18. (*a*) McLean, J. M.: Direct Surgery of Paretic Oblique Muscles, Arch. Ophth. **42**:50 (July) 1949. (*b*) Lee, O. S., and O'Brien, C. S.: Surgical Treatment of Concomitant Strabismus, ibid. **42**:178 (Aug.) 1949. (*c*) Scobee, R. G.: Degrees of Correction per Millimeter of Surgery, Am. J. Ophth. **32**:1376 (Oct.) 1949. (*d*) Burian, H. M.: The Principles of Surgery of the Extraocular Muscles, ibid. **33** (pt. 1):380 (March) 1950.

19. Scobee, R. G.: Intermittent Exotropia, Tr. Am. Acad. Ophth. **53**:658 (July-Aug.) 1949.

on the globe. However, he listed situations in which a relatively greater result from the operation could be expected. This list included heterotropias of short duration, variability in the angle of squint, deviations on which glasses have a marked effect and intermittent heterotropias. One would gain the impression that the effect of operation is generally greater, the less stable the deviation, i. e., the more preponderant the innervational factors. [This opinion is not in agreement with my experience or with the statement of Scobee himself that the operative result is greater in patients with large deviations and monocular heterotropias—conditions which make for a stable angle of squint—than in patients with small deviations or alternating heterotropias.]

I [18d] have presented a detailed discussion of the principles of surgery of the extraocular muscles, derived from the fundamental tenet that innervational factors should be treated by nonsurgical means and that surgical intervention, which can directly influence only the mechanical conditions, should be reserved for the noninnervational factors. Normalization of the rotation of the eyes should be the goal of surgery, and abnormalities in the behavior of the rotations should therefore be the decisive factor in the choice of surgical therapy.

Piper [1] holds a comparable view. In accordance with the three stages which he distinguishes, he advocates nonsurgical treatment in the dynamic stage, tenotomies in the concomitant stage and resections in the anatomically fixed stage.

A general review of the surgical management of strabismus, with numerous valuable practical hints, has also been given by Post.[20]

A paper favoring advancements over recessions is published by Harms.[21] His arguments are essentially the same as those of all advocates of advancement since the days of Landolt. It is interesting to note that Harms warns against combined operations but reports encouraging results with partial tenotomies of the antagonist of the resected muscle, a practice much used and recommended by Lancaster.

The effect of surgical treatment for strabismus on the binocular cooperation of 100 patients is reported by Stanworth.[22] Sixty of these patients had no binocular vision prior to operation, and 40 had only simultaneous macular perception. Fifty-one of the 100 patients had preoperative orthoptic training, without beneficial result. Of the 60 patients without binocular vision, 9 obtained fusion with amplitudes, and 7 of these developed stereopsis. Of the 40 with simultaneous macular perception, 17 obtained fusion with amplitudes and 13 of these developed

20. Post, L. T.: Suggestions for the Surgical Management of Strabismus, Am. J. Ophth. **32**:345 (March) 1949.

21. Harms, H.: Ueber Muskelvorlagerung, Klin. Monatsbl. Augenh. **115**:319, 1949.

22. Stanworth, A.: The Final Result of Squint Operations in Which Restoration of Binocular Vision Was Not Expected, Brit. J. Ophth. **33**:477 (Aug.) 1949.

stereopsis. For a favorable functional result, the vision of the two eyes had to be approximately equal; no patient with anisometropia of over 1.5 D. developed fusion. The size of the preoperative angle appeared to have no effect on the postoperative functional result, but the importance of the postoperative angle was all the more striking: In all but 2 of the patients developing fusion the residual angle was 5 degrees or less. Stanworth's results appear to be amazingly good. One wonders how they compare with results from other clinics. It is regrettable that Stanworth has not included in his paper any information about the direction and type of the deviation of the eyes of his patients.

The occurrence of intraocular infections after muscle surgery has led Zarrabi [23] to devise a curious method of operating on the ocular muscles which avoids their being anchored in the sclera. Instead, the sutures are secured by their being placed through the skin of the lids on the side opposite the muscle operated on after they had been passed below the conjunctiva. It is doubtful whether this method will achieve great popularity.

Because of the frequent combination of vertical and horizontal deviations, papers dealing with the surgery of the oblique muscles will be briefly mentioned. The interest in the direct surgical approach to the oblique muscles has increased a great deal in the last few years. The literature is exhaustively discussed by Loutfallah,[24] who also reports on his personal experiences with recessions of the inferior oblique muscle at its insertion. Personal experiences with this type of operation are also related by Lloyd,[25] who found that in 48 of 100 cases in which operation was performed for horizontal strabismus the squint was combined with vertical defects requiring operation. This number is remarkably high. It is interesting to compare it with the percentage given by Meesmann,[5] who found that in his large material vertical deviations were present in 8 to 10 per cent of cases. It is hardly likely that this difference is due to geographic or racial differences, but, rather, that it results from differences in diagnostic method and clinical judgment.

McLean,[18a] in writing on the direct surgical treatment of the paretic inferior oblique muscle, gives a detailed account of the technic he employs. Of the many interesting details of this paper, I should especially point out McLean's statement, with which I fully agree, that in all satisfactory cases the appearance in the immediate postoperative period should be one of pronounced overcorrection. Failing this, the final result may be expected to be an undercorrection.

520 Commonwealth Avenue (15).

23. Zarrabi: L'opération du strabisme, Arch. d'opht. **9**:732, 1949.

24. Loutfallah, M.: Chirurgie du petit oblique, Ann. d'ocul. **182**:81 (Feb.) 1949.

25. Lloyd, I.: Recession of the Inferior Oblique, Brit. J. Ophth. **33**:291 (May) 1949.

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Plastic Surgery Award.—The Foundation of the American Society of Plastic and Reconstructive Surgery offers as its 1950 award $500 (first prize of $300; second prize of $200) and a certificate of merit for essays on some original unpublished subject in plastic surgery.

Competition shall be limited to residents in plastic surgery of recognized hospitals and to plastic surgeons who have been in such specific practice for not more than five years.

The first prize essay will appear on the program of the forthcoming annual meeting of the American Society of Plastic and Reconstructive Surgery, to he held in México D. F., Mexico, November 27 to 29, 1950. Essays must be submitted before Aug. 15, 1950.

Communications should be addressed to the secretary, Dr. Clarence R. Straatsma, 66 East Seventy-Ninth Street, New York.

Ophthalmologist Wanted for United States Public Health Service Program.—The United States Public Health Service is conducting a nationwide program on the control of chronic diseases. The conservation of vision is an integral part of this program. To this end, the Public Health Service has created the position of Chief of the Sight Conservation Program. The man selected will have the responsibility of developing a new type of public health program and would have available the help and experience of men who have developed similar programs in other fields. The appointee should be a certified ophthalmologist and will be appointed on a full time basis, either as a regular or a reserve commissioned officer in the United States Public Health Service. The grade and remuneration depend on the age of the appointee, the salary varying from $5,686 to $9,984 per annum.

Any interested ophthalmologist should communicate directly with Dr. A. L. Chapman, United States Public Health Service, Federal Security Agency, Washington 25, D. C.

Obituaries

MANOEL A. DA SILVA, M.D.

1913-1950

Unexpectedly, as the result of a sudden heart attack, Dr. Manoel A. da Silva passed away on March 5, 1950. A member of the modern generation of Brazilian ophthalmologists, Manoel A. da Silva, although still a young man, was well known not only in São Paulo, but in Brazil and the Americas.

Born in São Paulo, he attended grade school and high school in his native city, registering in 1933 at the Escola Paulista de Medicina and graduating with the first class from that school, in 1938. His spirit and capacity for work and organization helped him to make friends among his colleagues, and these same qualities aided his advancement in his professional career.

During his last year at school he worked as monitor in the ophthalmologic clinic of the Escola Paulista de Medicina and was afterward appointed assistant and instructor, helping not only with the teaching of undergraduates but also in the graduate and postgraduate training in ophthalmology.

When the scholarships of the W. K. Kellogg Foundation and Pan-American Association of Ophthalmology were established, Manoel A. da Silva won first place among the Brazilian candidates and spent a year at the Illinois Eye and Ear Infirmary, at the time when Harry Gradle and Peter Kronfeld were teaching there, later visiting several other clinics in the United States. When the Society of Kellogg Fellows was founded, he was elected president.

He practiced ophthalmology with proficiency and extraordinary devotion. He was president of the Centro de Estudos de Oftalmologia de São Paulo and vice president of the Sociedade de Oftalmologia de São Paulo. He read the official paper at the fourth Jornadas Brasileiras de Oftalmologia in Porto Alegre and had been chosen by the Sociedade de Oftalmologia de São Paulo and by the Centro de Estudos de Oftalmologia to present the official paper of these societies at the fourth Pan-American Congress of Ophthalmology. He was an assistant editor of *Ophthalmologia Ibero Americana*, a journal which owes a great deal to Manoel da Silva for his tireless labor. He cooperated enthusiastically in the organization of the bulletin of the Centro de Estudos de Oftalmologia and always entered wholeheartedly into all the activities of the ophthalmologic clinic of the Escola Paulista de Medicina.

Manoel A. da Silva's value can be gaged by the great void left when he passed away and by the general consternation caused by the news of his death.

In memory of his services as the assistant executive secretary, a position he had held since 1948, the Pan-American Congress of Ophthalmology, at a meeting held at Miami Beach, paid a significant tribute to him, thus expressing the sorrow of all ophthalmologists of this hemisphere on his premature death.

Moacyr E. Alvaro.

Society Transactions

EDITED BY DR. W. L. BENEDICT

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Perce DeLong, M.D., *Chairman*
M. Luther Kauffman, M.D., *Clerk*
Oct. 21, 1948

Optochiasmatic Arachnoiditis: Report of a Case. DR. MORGAN B. RAIFORD (by invitation).

An 8 year old white boy was admitted to the Graduate Hospital of the University of Pennsylvania on June 15, 1948, with the chief complaint of poor vision in both eyes, which was first noted in December 1947. He had no history of any intercurrent disease, either ophthalmic or systemic, other than a contusion of the forehead, the result of a fall in October 1947, without any immediate noticeable effect. When he returned to school after the Christmas vacation, he noticed that he was unable to see the blackboard, but he was aware of no other symptoms. He was hospitalized from the middle of February to the middle of April 1948, and treatment consisted of six injections of typhoid vaccine and administration of multiple vitamin preparations. The diagnosis at that time was optic neuritis. Studies of the spinal fluid were repeated in another hospital, with similar findings. The patient's visual defect gradually increased (mother's statement) up to the time of hospitalization, in June 1948.

The family history was noncontributory. There was a history of tonsillectomy at the age of 5 years and of dull, diffuse headaches in November and December 1947. He had had no headaches or other disturbances, except for gradual loss of vision, since December 1947.

General physical examination on his admission to the hospital revealed nothing abnormal. Vision was *2/60* in each eye and was not improved with glasses. The visual fields showed concentric contraction of the peripheral fields with slight enlargement of the blindspots. There were no scotomas. Examination of the fundus showed the disks to be pale and the margins blurred. There was no papilledema. The retinal vessels were normal and the macular areas slightly pigmented. There were no retinal hemorrhages or exudates. A neurologic examination by Dr. Joseph Yaskin did not reveal any other abnormalities.

On June 18, 1948, roentgenograms of the skull, orbits, sella turcica and optic foramens revealed nothing abnormal. A ventriculogram, done on June 29, 1948 by Dr. Finkelstein, was reported on as follows: "Only a small portion of the third ventricle is visualized, and this is of normal size. The fourth ventricle is not visualized. No air can be seen in the basal cistern or in the subarachnoid pathways. A lesion of the posterior fossa, such as a tumor or basal arachnoiditis, cannot, therefore, be excluded.

In view of these findings, a craniotomy in the right frontoparietal area was done by Dr. Robert A. Groff on July 6, 1948, revealing chronic arachnoiditis around the optic nerves and the optic chiasm. These fibrous bands and adhesions were incised, and the optic nerve was freed. The patient made an uneventful recovery and was discharged on July 13.

The patient was last seen on Sept. 15, 1948, at which time the visual acuity was 6/30 in the right eye and 6/7.5 in the left eye. The visual improvement has been noticeable to the patient, and he has been able to read without any difficulty.

DISCUSSION

Dr. Robert A. Groff: The condition has been verified by operation in other cases. However, I do not believe that there are any recorded cases of a patient so young in which the lesion has been verified by operation. Arachnoiditis is an entity. It occurs primarily around and near the optic chiasm and secondarily about the cisterna magna in the posterior fossa, frequently simulating tumor in both situations. This condition was referred to by Dr. Frazier as pseudotumor.

The diagnosis is extremely difficult, and I believe is made only at the operating table. In my opinion, it cannot be made clinically with certainty, but it can be tentatively and confirmed at operation. The decision to operate is a difficult one, for the operation is serious. However, one weighs the risk against the fact that vision is extremely important to the patient. The entire matter must be put before the family, with the idea that the patient's vision may be regained or not, depending on what is found. In this case, we were fortunate in finding a thickened arachnoid, which was removed from the region of the optic chiasm. The subsequent course showed that the arachnoiditis had been the cause of the visual defect.

Secondary Functions of the Inferior Oblique Muscle. Dr. William E. Krewson III.

The literature was briefly reviewed, with comments on the confusion regarding the manner in which the inferior oblique muscle moves the eye. Drawings in perspective portraying the muscle plane and the location of the muscle were shown for various positions of rotation. The action generally attributed to the inferior oblique muscle is primarily that of extortion, which increases as the eye is rotated externally, together with the secondary, or subsidiary, functions of elevation, which increases as the eye is turned inward, and external rotation, which increases as the eye is rotated outward. On the basis of the anatomic data of Volkmann, it is concluded that variations in these generally accepted actions apparently exist. Both the primary function of extortion and the secondary action of elevation can be shown to have their maximum effect when the eye is turned outward 7 degrees, while at this position the horizontal rotating effect is nonexistent. As the eye is turned outward beyond this position, the inferior oblique muscle becomes an external rotator; and as the eye is turned inward from this position, the muscle acts as an internal rotator. The manner in which the muscle actually functions depends on its angular attachment to the globe. Probably these opposing views can be reconciled on the basis of the considerable variation which is known to exist in the anatomic relations of the extraocular muscles.

DISCUSSION

DR. FRANCIS HEED ADLER: This careful study by Dr. Krewson is one of the best arguments one has for abandoning the old concept of a primary, secondary and tertiary action of each of the ocular muscles. This may have been a convenient way of teaching the various components of pull of each of the muscles, but it leads to false conceptions.

Dr. Krewson's studies show that the inferior oblique has one action in one position of gaze and a diametrically opposite action in another position. The same is true not only of the inferior oblique, but of the superior oblique and both the superior and the inferior rectus muscles. One thinks of the superior rectus as an adductor, and it is, in the primary position of gaze; but when the eyeball is abducted 23 degrees from the primary position, the muscle loses its adduction as one of the components of its pull, and when the eye is rotated outward beyond this point, it then becomes an abductor.

I think one must accept the studies that have been made showing that there is no center of rotation of the globe. The studies of Park and Park and of Verrijp and others have proved conclusively that there is no such ideal condition as a central point of rotation about which the eye moves. The eye makes transitory movements laterally, forward and backward and up and down, and the centers of rotation cover an area of a few millimeters. For this reason, it is extremely difficult to make calculations which determine in just what position the inferior oblique muscle becomes an adductor instead of an abductor. In muscle physiology it is often overlooked that in all ocular movements more than one muscle contracts. In the lateral versions, for example, five muscles in each eye are cocontracting simultaneously. In dextroversion, the lateral rectus muscle of the right eye acts sufficiently as an abductor at the start. In this position it has a long arc of contact and works at a mechanical advantage. The superior and inferior rectus muscles in this position cocontract and keep the eyeball from moving up or down. They also act as adductors in this position, but this adduction is balanced by the cocontraction of the two oblique muscles, which keep the vertical meridian erect and, by their abducting effect, counterbalance the adducting effect of the superior and inferior rectus muscles. As the movement progresses, the lateral rectus acts to an increasingly greater disadvantage. When the eyeball has passed 23 degrees of abduction, the superior and inferior rectus muscles become abductors, and they, together with the oblique muscles, are largely responsible for the further abduction of the eye. This fact explains the *modus operandi* of the Hummelsheim operation, and probably all modifications of it. By transplanting part of the superior and inferior rectus muscles to the attachment of the lateral rectus, one makes these muscles abductors by their cocontraction, and this abduction takes effect at the very beginning of dextroversion.

These studies by Dr. Krewson are of vital interest and should eradicate from textbooks the idea that each ocular muscle has three separate functions.

DR. WILLIAM E. KREWSON III: I want to thank Dr. Adler for his informative discussion. His criticisms are well taken, and quite justified. It is true that there is no fixed center of rotation, and that the centers of rotation are not identical with the anatomic or geometric center of the

globe. Variations due, for example, to the check ligaments and to Tenon's capsule are also factors, but probably none greatly affects the over-all picture.

It is also true, as I intended to mention but failed to do, because of limited time, that no one muscle acts on the globe independently or at any one time. I did not wish to imply that the muscle, the inferior oblique in this case, actually and independently turned the eye to the positions indicated; rather, my purpose in the analysis is to show how the energy of the muscle is expended on the globe, or how the muscle really acts when the eye is already rotated in the various positions mentioned.

Syphilitic Primary Optic Atrophy as a Cause of Blindness: Importance of Early Diagnosis. Dr. Joseph V. Klauder, Dr. George P. Meyer and Dr. Benjamin A. Gross (by invitation).

In a brief résumé of the literature on the frequency of syphilis as a cause of blindness, it was stated that 10 to 15 per cent of blindness is due to syphilis. The importance of this disease in connection with blindness in the United States is evident, for there are between 20,000 and 30,000 cases of blindness resulting from syphilis, optic nerve atrophy being the immediate cause in most cases.

The authors presented a study of 397 cases of syphilitic primary optic nerve atrophy, congenital syphilis being the causative factor in 20 cases and the acquired form in the remainder.

The factors discussed were the relation to age, sex, race and type of disease; the character of antisyphilitic therapy before the onset of optic nerve atrophy (treatment was shown to be deplorably inadequate); the patient's visual acuity on his admission to the clinic (61 per cent were industrially blind or worse); pathogenesis (the inflammatory origin is generally accepted); symptomatology (stress is laid on diplopia and leg pains as prodromal, and loss of vision and field changes as early, symptoms, with accompanying neurosyphilitic signs), and diagnosis (a field defect is probably the earliest sign). Loss of central acuity and pallor of the disk usually appear later and indicate advancing, and usually irrevocable, changes.

Syphilis is a frequent cause of blindness, approaching cataract and glaucoma in importance. Ophthalmologists are urged to be alert to the early diagnosis of this condition, for early recognition of the condition holds the only promise of amelioration or arrest.

This paper was published in full in the *American Journal of Syphilis, Gonorrhea and Veneral Diseases* (**32**: 574 [Nov.] 1948).

DISCUSSION

Dr. Joseph V. Klauder: In addition to the rather pessimistic data presented by Dr. Meyer in the first part of the presentation, one could draw similar deductions from the following figures: Before the war the incidence of new cases of syphilis in the United States, as calculated by the United States Public Health Service, was about 500,000 per year. That incidence decreased until shortly after the war (1945), when it increased slightly, and is now estimated as about 250,000. It is thought that of the new cases of syphilis, tabes dorsalis will develop in about 5

per cent if treatment is not given or is inadequate, and that of this number optic nerve atrophy will develop in 10 to 15 per cent. This estimate applies only to cases of tabes dorsalis, not to the approximately 40 per cent of cases of optic nerve atrophy associated with neurosyphilis other than the tabetic form.

Dr. Meyer has presented our rather unfortunate experience in the early diagnosis of optic nerve atrophy at Wills Hospital. The figures he presented—61 per cent of patients were industrially blind when first seen—are certainly not gratifying. What can be done about it? The importance of syphilis as a cause of blindness needs no emphasis. It is worthy of the attention of every physician who treats syphilis. The ophthalmologist is particularly concerned with syphilis as a cause of blindness. We appeal to ophthalmologists for more interest in syphilis as a systemic disease, in its public health aspects, in its treatment and in the early diagnosis of optic nerve atrophy. We believe that Berens and Goldberg implied this in their report (Syphilis in Relation to the Prevention of Blindness: A Study of 100,000 Case Records, *J. A. M. A.* **109: 777-781** [Sept. 4] 1937), in which they stated that there was often insufficient attention to the history, examination, serologic tests and treatment of patients whose ocular disease was syphilitic.

Optic nerve atrophy occurs in patients whose neurosyphilis usually pursues a silent course. It is infrequently associated with the classic symptoms of tabes dorsalis—dysuria, ataxia and severe leg pains. In our study, the two most frequent symptoms preceding subjective loss of vision were diplopia and leg pains. Diplopia was usually transitory and preceded, frequently by years, the loss of vision. Leg pains were usually mild and their presence was elicited only by direct questioning. Optic nerve atrophy occurs predominantly in patients who are ignorant of their infection and who have had no antisyphilitic treatment. Unfortunately, the major symptom that leads to diagnosis is impaired vision.

Ten years, at least, elapse after infection before optic nerve atrophy develops; the usual interval is eighteen years. There must be a period, preceding pallor of the nerve head and impairment of visual acuity, in which perimetric studies would reveal early field defects. From our study, we believe that that period may range from a few months to several years. We would stress that interval as a propitious one for the early diagnosis of optic nerve atrophy. To accomplish this, routine ophthalmoscopic examination must be made on every patient with syphilis of more than ten years' duration, certainly on every patient with neurosyphilis. It is to be recalled that pupillary abnormalities are common symptoms of neurosyphilis, appearing early and constituting a "short cut" in clinical diagnosis.

Bruetsch observed basilar meningitis as part of optic nerve atrophy, existing in the absence of other evidence of neurosyphilis. The clinical diagnosis of syphilitic optic nerve atrophy is therefore justified in a case of syphilis without evidence of neurosyphilis. In our experience, however, such an occurrence is rare.

To facilitate the early diagnosis of optic nerve atrophy, ophthalmologists and all physicians who examine patients with syphilis should have a high degree of awareness of the possibility of involvement of the optic nerve. In records of private, ward and clinic patients, too infre-

quently no mention is made of examination of the optic nerve unless the patient has complained of visual loss. Ophthalmologists are admirably situated to determine the existence of optic nerve atrophy in every patient with syphilis of several years' duration, at least those with pupillary abnormalities.

The ophthalmoscope and the perimeter should be added to the list of instruments—dark field microscope, lumbar puncture needle, x-ray apparatus and electrocardiograph—of vital importance in the diagnosis of syphilis.

DR. LOUIS LEHRFELD: In 1937 there was prepared from data at the Wills Hospital a survey of cases of optic nerve atrophy due to syphilis (Lehrfeld, L., and Gross, E. R.: Statistical Investigation of Syphilitic Atrophy of the Optic Nerve, ARCH. OPHTH. **18:** 666 [Oct.] 1937), covering a period from 1926 to 1937, inclusive. A total of 522 cases were studied, in all of which there had been some degree of optic nerve atrophy. It is gratifying, indeed, to find that the statistics of the present investigators, Drs. Klauder, Meyer and Gross, are comparable to those which we reported in 1937. In that survey I aimed to find out what happened to patients with optic nerve atrophy. Did they get well? Did they get worse? Was the treatment effective in controlling the optic nerve atrophy?

In reading Duke-Elder's textbook, I was reminded of the statistics in which he quoted me as follows: Of the untreated patients, 74 per cent were blind within three years; all were blind within five years. Of the patients with optic nerve atrophy receiving the well known methods of antisyphilitic treatment at that time, 24 per cent became blind within five years, and all of them were blind within eight years. This was damaging evidence that the method of treatment at that time was not sufficient to control, to cure, or even arrest, syphilitic optic nerve atrophy. I had hoped that the authors would give us some information on therapy. Despite the fact that we stress the early diagnosis of optic nerve atrophy, our methods of treatment are insufficient and inadequate to control the optic nerve atrophy of syphilis. What modifications of the present methods do the authors suggest to bring about a control of optic nerve atrophy, or at least to reduce the incidence of blindness from this disease?

I wish to call your attention to an article published by Dr. Melvin Knisley and associates, in Chicago (Sludged Blood, *Science* **106:** 431 [Nov.] 1947), in which he spoke of blood sludging in various diseases. He stated that in malaria and in various inflammatory and infectious diseases the rubricytes (red blood cells) become sticky and agglutinate. Dr. Knisley has probably opened up an entirely new field in the pathology of optic nerve atrophy due to syphilis, that of the blood sludging in the end arteries of the retina. The question I wish to put to the investigators is this: Is there anything to control optic atrophy if it is diagnosed early? Are the present therapeutic agents—penicillin and the heavy metals—sufficient to control optic nerve atrophy, or are we going to lean on Dr. Knisley for another suggestion on how to prevent blood sludging and thereby prevent atrophy of the optic nerve?

DR. JOSEPH V. KLAUDER: One cannot answer Dr. Lehrfeld arbitrarily, for there is so much variability in the course of syphilitic optic nerve atrophy. All are familiar with cases of the rapidly progressive

disease that pursues a downhill course regardless of treatment, terminating in blindness in one year or less. In cases of the slowly progressive disease, the prognosis is more favorable. Except in cases of the rapidly progressive form, we do not believe that the inevitable result is blindness. We have a number of patients in the clinic whose atrophy has remained stationary for periods of observation as long as eighteen years. We observed this in patients who had received different methods of treatment.

Certainly one is justified in being less pessimistic about the prognosis now than years ago—that era, for example, when the disease was treated with strychnine. There has been a considerable addition to the therapeusis of the disease. Fever therapy, especially with malaria, is to be stressed. The status of penicillin therapy awaits evaluation.

DR. GEORGE P. MEYER: I think we have shown the importance of the early diagnosis of optic nerve atrophy, for with well advanced disease the outlook is rather poor. I remember that when Dr. Lehrfeld's article came out I felt depressed about the prognosis. At that time I had a patient with neurosyphilis and beginning optic nerve atrophy, and I asked a colleague, a local syphilologist, to undertake the treatment of syphilis. He only shrugged his shoulders and said, "Oh well, they all go blind anyway"—and he was associated with one of the larger teaching institutions in Philadelphia. The patient was subsequently referred to Dr. Klauder, and he still has vision. Dr. Klauder did not have such a pessimistic outlook with regard to treatment. I believe that the first bright note was struck by the Baltimore investigators. I do not remember the figures exactly, but there was a direct ratio between the prognosis and the amount of vision that was retained when a patient first reported for treatment. If a patient was industrially blind when he first reported for treatment, the outlook was poor; so it is that one gets figures like Dr. Lehrfeld's and Duke-Elder's who report that within eight years all patients become blind. That certainly is not the experience in our clinic, for there are many patients who still have useful vision eight or ten years after the diagnosis of optic nerve atrophy. The first person who should be reminded of that is the pessimistic ophthalmologist. Get him to feel that by his being alert in making an early diagnosis valuable vision may be saved for the patient.

Perce DeLong, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

Dec. 16, 1948

Plasma Cell Myeloma of the Orbit: Report of a Case. DR. JOSEPH J. McEVOY (by invitation).

Tumors consisting of plasmocytes occur frequently in the bone marrow and constitute one of the histologic types of multiple myeloma. Extramedullary plasmocyte tumors, on the other hand, are of greater rarity.

A total of 128 cases of extramedullary plasmocyte tumors have been described in the literature. Most of these tumors have involved the mucous membranes. The commonest site of occurrence is in the

mucous membrane of the air passages, and the next commonest site, in the conjunctiva, where 47 such tumors have been recorded. The only case of plasma cell myeloma involving the orbit, other than the one described here, is that described by Walsh, which he reported in his textbook on neuro-ophthalmology.

Histologically, the abundance of plasma cells is the salient feature of these tumors. The tumor cells are characterized by a large amount of cytoplasm and an eccentric nucleus. The chromatin is arranged in cart wheel fashion, and a paranuclear unstained area is present. Cells with two, three or more nuclei are common. Other cells, such as segmented granulocytes, lymphocytes and monocytes, if present at all, are never an essential part of the tumor structure.

When an isolated plasmocytoma is found, there arises the question whether it is a solitary benign lesion, easily removed, or a part of the very malignant multiple myeloma. It seems that the microscopic appearance does not play an important role in predicting the clinical course of a given lesion. Even the appearance of mitotic figures in the cells does not indicate malignancy. As long as the plasmocytoma is localized and confined to soft tissues, and there is no other clinical evidence of multiple myeloma, cure can generally be obtained.

The case to be presented is that of a white woman aged 80 who was admitted to the medical service of the Philadelphia General Hospital on May 26, 1948. She had no complaints and was admitted simply for custodial care until admission to a nursing home could be arranged.

Physical examination revealed a well developed but poorly nourished, anemic elderly woman. General physical examination revealed nothing of note other than the anemia, which was hypochromic in type and was thought to be nutritional. The right eye was blind. She had had a cataract extraction three years previously. The cornea was densely leukomatous. The left eye showed a senile cataract with vision of 6/60. There was a swelling of the right lower lid, and a firm mass, extending into the orbit, was felt on palpation. This mass had been present about three months, was painless and was slowly progressing in size. There was no exophthalmos.

On June 16, 1948 operation was performed with the use of local anesthesia. The lower lid was incised along its entire length below the tarsus. Nothing was found in the lid itself. Within the septum orbitale was a reddish, firm mass with a smooth, apparently encapsulated surface. By blunt dissection it was possible to separate the mass from the surrounding tissues and to follow it back into the orbit beneath the globe. After being shelled out and removed *in toto*, it measured 3 by 1 by 1 cm. A large amount of hemorrhage occurred and was controlled with difficulty. A pressure dressing was applied. After operation a rather large hematoma developed at the operative site.

The pathologic report on this tumor follows: The material consisted of a homogeneous mass of uniformly dark round cells—plasmocytes. There was almost no stroma, and practically no mitotic figures were seen. The diagnosis was plasma cell myeloma.

Roentgenographic examination of the skull, the orbit, the vertebrae, the ribs and the pelvis showed no evidence of bony myelomatous involvement. Repeated urinalyses did not reveal Bence Jones protein. The

serum calcium was 10 mg. per hundred cubic centimeters. Examination of the sternal bone marrow showed no increase in cellularity, and hematopoiesis was essentially normal. There was spotty infiltration throughout, with well differentiated plasmocytes.

The serum protein was 10.7 Gm. per hundred cubic centimeters; of this, 2.4 Gm. was albumin and 8.3 Gm. globulin.

This extreme degree of hyperglobulinemia was thought to be suggestive of a diffuse myelomatous process, in spite of the other negative findings.

The patient's right orbit was treated with two courses of radiation, of three doses each, given at three day intervals, the doses of roentgen radiation being 300, 600 and 900 r.

The postoperative hematoma was completely absorbed in two weeks. No remaining tumor was discernible, and the patient was discharged from the hospital to a nursing home on August 24.

This case was presented as illustrating an unusual orbital tumor and the difficulties of evaluation and prognosis of isolated plasma cell tumors.

DISCUSSION

DR. THOMAS COWAN: The case illustrates well the difficulty of making a diagnosis before excision. Clinically, the tumor impressed me as being benign by its appearance in the lid, and it had been so diagnosed elsewhere. As the orbit was entered, the characteristics of the tumor became more and more those of a sarcoma. At its inner attachments it had so infiltrated the tissues that it was removed with difficulty. The postoperative healing was excellent for such an infiltrating tumor.

DR. PERCE DELONG: Plasmocytoma is not rare. However, few have been reported in the orbit.

The plasmocytes are not easily recognized because pathologically they present immature forms of the typical plasmocyte, and for this reason they are often referred to as myeloma cells.

The metabolic aspect of myelomatosis is interesting, in that it produces a protein in the urine which must be differentiated from albumin by the Bence Jones test. If found, the diagnosis is conclusive. However, its presence is intermittent.

DR. JOSEPH MCEVOY: We tested for the Bence Jones protein several times, and there was none found, but the serum globulin was extremely high.

Endothelial Myeloma (Ewing's Tumor) of the Orbit: Report of Two Cases. CAPT. FRED HARBERT (MC), U.S.N. (by invitation) and COMDR. GEORGE L. TABOR JR. (MC), U.S.N. (by invitation).

DISCUSSION

DR. PERCE DELONG: Endothelial myeloma is not considered a pathologic entity by the majoirty of pathologists. It produces the syndrome of a nonosteogenic, round cell, radiosentitive tumor, and this syndrome can be produced by many types of tumors.

Analysis of cases of this growth by many prominent pathologists has shown that in the majority the tumor was the expression of metastasis. In the child and in the adolescent the tumor was not truly endothelial myeloma but a neuroblastoma, which proved to be metastatic; finally, the tumors that were primary proved in almost all instances to be reticulum cell sarcoma. In Dr. Harbert's second case the final diagnosis was reticulum cell sarcoma. Endothelial myeloma (Ewing's tumor) is not an entity but a syndrome.

CAPT. FREDERICK HARBERT (MC), U.S.N.: I must, of course, defer to Dr. DeLong's greater experience and judgment, but, from the standpoint of the clinician, I think that endothelial myeloma, or Ewing's tumor, is still a tenable diagnosis. What are you going to call the characteristic bony lesion when a primary soft tissue tumor cannot be found, either at operation or throughout the subsequent course of the disease? Ewing himself made the absence of primary tumor a criterion for diagnosis; so at least it is a working diagnosis and may have to remain even after autopsy. The differentiation of Ewing's tumor and reticulum cell sarcoma is considered largely academic.

Diffuse Infiltration of the Iris Associated with Nevoxanthoendothelioma: Report of a Case. DR. GRACE R. NACHOD (by invitation).

The clinical and histologic pictures of nevoxanthoendothelioma were discussed, and a case was reported.

A Negro male infant was first seen because of a sore eye, which proved to be due to diffuse cellular infiltration of the iris and ciliary body with dislocation of the lens and secondary glaucoma. Shortly after the eye was enucleated, there developed multiple lesions of the skin; biopsy of one led to the diagnosis of nevoxanthoendothelioma.

Although the cells that had infiltrated into the iris and the ciliary body were somewhat similar to those seen in the cutaneous lesion, no definite conclusions as to their actual relation could be drawn.

DISCUSSION

DR. JOHN PORTER SCOTT: I speculate on what would have happened if this eye had not been removed. These lesions in the skin have the tendency to regress and disappear, leaving no greater scars than does chickenpox.

When I saw this child at the time the cutaneous lesions first appeared, I thought that the eye had not been removed soon enough, for in my ignorance I assumed them to be metastatic lesions. At that time I had not received Dr. Fry's excellent description of the tumor and was not sure of the surgical diagnosis.

Lesions of this type occur in some forms of storage disease. One of these is uncontrolled diabetes, in which xanthomatous lesions may appear. Such lesions are yellower and less pink or salmon than were the lesions in this case. As in this condition, they may disappear. In Hand-Schüller-Christian disease the lesions are yellowish and larger and have no tendency to disappear.

This case represents unexplored ground. I could not find any case in the literature of the ocular occurrence of the tumor. In 1 case

reported a tumor was in the orbit. Ophthalmologists should remember the appearance of this tumor. One would be extremely optimistic to think that this tumor would have regressed, as did the cutaneous lesions.

Dr. W. E. Fry: Several features of the ocular specimen bear emphasis. The first is the infiltrate in the iris, which was diffuse and dense, and in which there were giant cells of the Touton cell type, similar in appearance to the Touton giant cells that appeared in the cutaneous lesion, and which I understand are important in the diagnosis of the cutaneous lesion. The eye had been fixed and dehydrated in ether and alcohol; so it was not possible to carry out stains for fat. Fat stains of the specimen of skin showed a high degree of fat.

The other important feature was the anterior rupture of the retina through which, apparently, the dislocated lens had slipped. Just how this had occurred is speculative. One possibility is that the dislocation of the lens could have been produced artificially when the eye was cut prior to embedding. This is unlikely, for in hundreds of eyes that are cut, if they are cut with reasonable care, no dislocation of the lens occurs, and if it does occur the dislocation is not behind the retina. The secondary glaucoma, probably caused by the dislocation of the lens behind the anterior retinal dialysis, could have led to severe changes in the eye, so that enucleation was indicated.

The question arises as to whether these lesions of the iris regress. Probably they do, and that is why they have not previously been reported to any extent. In all probability, if the glaucomatous changes had not occurred, the eye might have cleared and the lesions have regressed spontaneously.

Dr. Herman Beerman: I know the history of this patient and the pathologic findings very well, for I had the opportunity to study the cutaneous specimen and Dr. Fry allowed me to study the section of the eye. Although Dr. Blank, Dr. Eglick and I have reported this case from the pediatric and dermatologic standpoints, I hope we have not interfered with Dr. Nachod's publication of the ocular findings.

This case is rare; there is only 1 other in the literature in which ocular complications have been noted, that reported by Dr. Ellis of Baltimore, in the discussion of the paper by Dr. Lamb and Dr. Lain. No further details are available on their case; therefore the present case is unique. I believe it is the first authentic instance in which both cutaneous and ocular complications have occurred and in which their identity was proved by pathologic examination.

I believe, in retrospect, that when one visualizes the amount of ocular damage one cannot say that the lesion of the eye would have regressed without performance of enucleation. I do not believe therefore, that any one who managed this case need fear criticism of the procedure employed.

Dr. A. G. Fewell: I thought the eye should be removed, the whole iris semed to be thickened and infiltrated with the growth. The intraocular tension was rather high, and the eye was apparently blind.

Dr. Grace R. Nachod: I am grateful to Dr. Fry, Dr. Fewell and Dr. Beerman for saying that they thought the enucleation was indicated.

General Anesthesia in Ophthalmology. Dr. H. H. Stone (by invitation).

DISCUSSION

DR. EDMUND SPAETH: Some time ago, in a discussion of anesthesia in ophthalmic surgery, an anesthetist, other than Dr. Stone, stated, "I do not understand the tremendous difference of opinion with regard to general anesthesia among ophthalmic surgeons; I doubt whether there is anything more chaotic in surgery." This observation has been made by other men. The fault, or perhaps the reason for that state of affairs, is not strange. Three factors are responsible. The ophthalmologist is concerned only with one of them, i. e., his willingness to consider each case for operation as an individual problem, and whether the operation indicated can best be performed with local or with general anesthesia. The second factor is the brief, but rather essential, physical examination by an attending internist and the consideration of his recommendation of the kind of anesthesia to be used. The third factor is the anesthetist's problem. Which type of anesthesia is to be used: inhalation anesthesia, intravenous anesthesia or rectal anesthesia? All have optimum indications for use; each meets best a given situation. It is seldom, in recent years, that the ophthalmic surgeon suggests the type of general anesthesia to be used. His wishes, however, should be considered as to whether the operation should be done with local or with general anesthesia; but the anesthetist and the internist are responsible for the type of anesthesia to be used in each case.

There is no doubt that the increase in the use of general anesthesia is directly proportional to the efficiency and the understanding of problems of ophthalmic surgery by the anesthetist. My colleagues and I feel unusually fortunate to have Dr. Stone for our surgical cases. Because of his efficiency and that of his department, we now view anesthesia quite differently. In the past, general anesthesia was used only when absolutely necessary. At present it has become the choice in many surgical procedures. Intraocular operations are still to be done with local anesthesia if possible; on the other hand, one need no longer dread such operations when general anesthesia is indicated, nor need one fear postanesthetic accidents and complications. This is quite a reversal in practice.

Plastic surgery, even the relatively minor procedures, can be done much better without infiltration and/or block anesthesia, otherwise necessary. Lacrimal sac surgery, with its rather exacting anatomic dissections, is simpler with general anesthesia. The operating time in all types of muscle surgery is shortened, regardless of the age of the patient, and the procedure is simplified without injections into the capsule sheath, which are necessary to make the operation painless. Surgical repair of retinal separation, which may require from a relatively brief period to hours on the operating table, when performed with the patient under general anesthesia is far less taxing to the patient and much easier for the surgeon.

These procedures need little, if any change in essential technics whatever the type of anesthesia. Intraocular surgery, however, when done with the patient under general anesthesia must have certain rather important changes in the surgical technic, associated with fixation of the globe and support of the lids. This applies particularly to corneal grafts; in fact, general anesthesia is so important with this operation that it is used also at the first dressing of the eye.

In the final analysis, a paper such as Dr. Stone's has greater significance to anesthesiology than to ophthalmology. The anesthetist cannot take care of ophthalmic patients unless the surgeon is willing to permit it and to cooperate with him. General anesthesia should play a greater role in ophthalmic surgery than it does, provided, of course, that trained medical specialists in anesthesiology are available.

DR. H. H. STONE: Up to the present my colleagues and I have had no fatalities. We occasionally get into difficulty; that happens regardless of the type of anesthesia. We have seen difficulty with local anesthesia—not in ophthalmic surgery, but we have had 2 fatalities in general surgery when local anesthesia was being used. The expert should give the anesthetic in ophthalmic surgery.

I feel that there is no more difficult operation than cataract extraction performed with general anesthesia, thoracic surgery being no exception. It takes far greater skill to keep the patient breathing, and yet not coughing or sneezing, when the cataract is removed, and to keep him well oxygenated during the entire procedure, than is required for a five or six hour pneumonectomy.

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Jan. 20, 1949

Abducens Paralysis Associated with Brucellosis: Report of Two Cases.
DR. JOSEPH C. YASKIN and DR. RUSSELL S. BOLES.

While abducens paralysis is a common occurrence, and is usually due to causes that are readily ascertainable, one occasionally encounters isolated paralysis of the external rectus for which there is no etiologic diagnosis. The idiopathic abducens paralysis is as rare as Bell's palsy is common. The diagnosis cannot be established until the patient makes a complete recovery.

Two cases of isolated abducens palsy due to brucellosis were reported. In both cases the agglutination tests gave positive reactions. In the first case the paralysis appeared several months after the acute stage of a severe infection, manifested by chills, fever, sweats, mild meningeal irritation and delirium. In the second case the abducens paralysis appeared ten days after an attack of headache, nausea and backache. Both patients made a complete recovery.

Brucellosis in its various forms is known to attack the nervous system, causing meningitis, meningoencephalitis and meningomyelitis, and occasionally neuritis of the cranial nerves. It is believed that the paralysis in our 2 cases was due to brucellosis.

It was suggested that among other causes of abducens paralysis one should consider the existence of latent brucellosis.

DISCUSSION

DR. RUSSELL S. BOLES: Paralysis of the sixth nerve is a not altogether uncommon disorder. These 2 cases are unique in that the cause appears to be brucellosis. This is a disease that exhibits no particularly specific lesions, but, as with most general nonspecific infections, it may affect various organs in a purely nonspecific way.

The three species of organism causing brucellosis are Brucella abortus, Brucella suis and Brucella melitensi. In the 2 cases reported, Dr. Yaskin and I cannot claim any credit for suspecting a relation between the paralysis of the sixth nerve and the infection. In the second case, which occurred in my private practice, I had no suspicion that brucellosis was the cause of the paralysis. I made the agglutination tests simply because of the patient's severe occipital headache and backache, profuse sweats, malaise and indisposition.

Brucellosis, as I said, exhibits no particularly significant lesions, but is protean in its manifestations, providing the various symptoms that I have described. In the first case, one with undulating fever, the paralysis of the sixth nerve did not develop for almost a year after the onset of symptoms, whereas in the second case it developed in ten days. The first was a case of the chronic type of the disease; the second, of the acute form. It is important to remember that the disease may be acute as well as chronic, although it is seldom recognized in its acute stages. The diagnosis of brucellosis may be made on the basis of the symptoms and laboratory findings. Blood cultures yield growth in about 25 per cent of cases. The blood agglutination tests give positive reactions in a high titer in most cases. The results of both of tests, however, may vary during the course of the disease.

The complications of brucellosis are varied. Arthritis is a common complication. Meningitis, as far as I have been able to gather, is not frequent, although I believe that Dr. Yaskin found, in a survey of the neurologic literature, that it was not an unusual complication. Pericarditis and subacute bacterial endocarditis occur. Uveitis is frequently seen in epidemic areas. The complication of unilateral sixth nerve paralysis is, I am sure, very unusual.

Dr. Joseph C. Yaskin: I have nothing to add except to emphasize that when one cannot find a satisfactory cause of paralysis of a lateral muscle one had best not call it idiopathic. In most cases isolated abducens paralysis eventually proves to be associated with widespread involvement of the nervous system. In the present discussion we have called attention to brucellosis. In the future, other infections or intoxications may be found to be the cause of abducens paralysis. It is well to keep an open mind before calling a given case idiopathic.

Sensitivity to Gold Ball Orbital Implant; Eczematous Contact Dermatitis Due to 14 Karat Gold: Report of a Case. Dr. H. Walter Forster Jr. (by invitation) and Dr. Robert F. Dickey (by invitation).

A woman aged 29 had enucleation of the left eye, for absolute glaucoma in 1939 with implantation of a 14 karat gold ball. During the next five years she had no symptoms. In 1944 a purulent discharge from the left orbit developed. Culture of this discharge yielded Staphylococcus aureus.

During the next two and one-half years the patient was treated with sulfathiazole, penicillin, sulfadiazine, potassium permanganate, staphylococcus ambotoxoid, tyrothricin and roentgen radiation of intermediate grade. The course was characterized by a fairly prompt response to each successive agent tried, with inevitable recurrence of the discharge from the left orbit a week or two later. No focus of infection was found,

though possible sources were extensively investigated. The purulent discharge recurred in such an inexplicable manner that malingering was suspected, but this could never be proved, even during hospitalization of the patient.

She was repeatedly seen in the staff conferences of the departments of ophthalmology and dermatology of the Hospital of the University of Pennsylvania. Finally, after two and one-half years of treatment, without success, the possibility of an allergic reaction to the implanted gold ball was suspected. Accordingly, the composition of the 14 karat gold was determined by communication with the manufacturer to be 60 per cent fine gold, 35 per cent copper and 5 per cent silver and tin.

Standard closed patch tests were made to the metallic components in question and to solutions of their salts. All gave negative results except those for gold salts and gold leaf. A 14 karat gold ball was obtained and placed in contact with the patient's forehead over the left orbit. A strong allergic reaction ensued.

It was then decided to remove the gold ball implant and to substitute for it a plastic ball, to which the patient was not sensitive, as shown by a preoperative patch test. This was done in April 1947. The operation was uneventful, and the orbit healed normally.

Because of the incredulity with which sensitivity to 14 karat gold was viewed, the ball removed from the patient's orbit was placed on her forearm in a dry gauze dressing, as a patch test. Twelve hours later the gold ball had to be removed because of severe local edema and vesiculation, with generalized urticaria over both arms and the face, neck, chest and back. The allergic reaction subsided in three days. Three days later the patch test was repeated on the other forearm because it seemed that a generalized dermal sensitivity was an unusual event. The same reaction occurred, subsiding in three days.

The patient was discharged to the outpatient department, where she has been followed since. At the time of this report, twenty-one months after removal of the gold ball, she has had no recurrence of the orbital discharge which made her life miserable for two and one-half years previous to removal of the gold ball.

No similar case has been reported in the literature.

Congenital Levator Palpebrae–External Rectus Muscle Associated (Internuclear) Reflex. DR. EDMUND B. SPAETH.

Two cases were presented to illustrate the possibility of an association existing as a reflex between the nuclei of the sixth and the third nerves. The author considered further the possibilities presented by these cases, i. e., the anatomic position for the development of congenital associated movements. This consideration included the cause of the Marcus Gunn phenomenon, as well as the various other associated oculomotor movements.

The paper will be published in its entirety.

DISCUSSION

DR. JOSEPH C. YASKIN: I am, and have for years been, bewildered by the neurology of the extraocular muscles, especially the abnormalities, for which there is no proved anatomic basis. Dr. Spaeth cited Tilney, Riley and Bing. Tilney and Riley wrote a magnificent book on the

structure and functions of the nervous system, and Dr. Riley has published valuable monographs on the extraocular muscles. Dr. Bing is a superb clinician, still practicing in Switzerland. These authors have made many statements regarding the anatomic connections of the various extraocular nuclei and nerves, but, to the best of my knowledge, microscopic verification of these statements is still lacking. One learns a great deal by inference and from comparative anatomy and embryology. Most of it, however, remains inference, and, because of the abstract nature of the material, I am not altogether clear about a great many phenomena. For many years, I have been trying to find out why the extraocular muscles escape in pseudobulbar palsy, in which most of the bilaterally innervated muscles of the head are involved. I have found no satisfactory explanation of this phenomenon in standard textbooks, in reference books or in discussions with men like Dr. William G. Spiller and the late Dr. Otto Marburg, who was my teacher of anatomy at the Neurological Institute of Vienna. I have spent many hours with Dr. Marburg trying to unravel the various connections of the extraocular nerve nuclei in the posterior longitudinal bundle, but we could find no satisfactory answer to many questions.

All that I have said does not detract from Dr. Spaeth's work in preparing this presentation. It is quite possible that, having become absorbed in the subject, he sees a great deal more in it than most of us can. For instance, he is much more familiar with the embryology of the various structures than are most of us. There can be no question of the validity of his observations. His interpretations appear to be sound in the light of present knowledge of the subject.

Finally, the recognition of these various syndromes is important, since it will lead to a better therapeutic approach.

Book Reviews

Toxic Eye Hazards. A Manual Prepared by the Joint Committee on Industrial Ophthalmology of the American Medical Association and the American Academy of Ophthalmology and Otolaryngology. Price $1. Pp. 101. The National Society for the Prevention of Blindness, Inc., Publication 494, 1790 Broadway, New York 19.

This is a manual prepared by a group consisting largely of engineers, physicists and chemists for the Joint Committee on Industrial Ophthalmology of the American Medical Association and the American Academy of Ophthalmology and Otolaryngology, intended to provide information on the causes, prevention, medical characteristics and first-aid treatment of industrial eye injuries from chemicals. It is intended that the manual be employed by both medical and lay personnel.

Chapter 1 presents a description and discussion of specifications and tests of the National Bureau of Standards and the National Safety Council concerning equipment for protection of the eyes. Advice is given for setting up an industrial eye protection program. Instructive charts and illustrations provide a guide to the selection of appropriate industrial eye-protective devices and furnish convincing evidence for the need of organized industrial eye protection.

Chapter 2 presents tables of chemical compounds and their effects on the eye. At first sight the lists are impressive by their length and promise of real usefulness to persons concerned with the effects of chemicals on the eyes. However, on closer inspection it is found that, although the chemical listings have been made with due regard to accuracy of chemical nomenclature, the descriptions of ocular effects are mostly reported in such inaccurate terms that the descriptions are not only frequently ambiguous but actually misleading. It appears that these lists have been compiled without the benefit of adequate ophthalmic knowledge, and one infers that the ophthalmologists on the sponsoring committee must not have examined the material with much care before publication. The responsibility of this committee to see that the ophthalmic aspects were accurately and adequately represented seems to have been neglected or ignored.

Thus one finds that, of 286 organic compounds listed, 127 are said to produce "necrosis." In some instances a clue is given that this refers to the cornea, but in most instances it is indeterminable what ocular tissue is supposed to be involved and to what degree. Rarely is the information given that this may mean merely the loss of some readily replaceable epithelial cells. Unfortunately, confusion worse confounded is achieved by frequent (92 times) inclusion with "necrosis" the term "keratoconus," with only occasional note that this is "experimental" and no note that the rabbit cornea (on which the original studies were made) is thinner than the human cornea and much more susceptible of distortion in healing. Somewhat less unfortunate, though vague, terms are "opaque cornea" (88 times) and "corneal burns" (45 times), which when unqualified as to depth, reversibility and species of animal are at best rather uninformative. In numerous instances chemicals are described as causing "iritis" (43 times) and "internal congestion"

(25 times), with no definition of what is meant by these terms. Also, no adequate warning is provided that these conditions were diagnosed largely in rabbit eyes and may well not characterize the usual response of accidentally exposed human eyes.

Little resolution of the confusion is to be gained from the bibliographic references, for the effects described for numerous compounds in the list are either not even in the articles referred to or are lacking in reliable substantiation in the source quoted.

Lack of adequate ophthalmologic supervision in the preparation of these lists has resulted not only in lack of discrimination in the use of technical terms but also in the failure of discernment of the significant features of injury, in contrast to the rare and trivial. Manifestations of toxicity which are poorly authenticated are given equal weight with the generally recognized manifestations. Typical examples picked from among numerous possible illustrations are noted: Carbon disulfide is listed as causing cataract, although no case presenting this condition could be found in the literature; under carbon monoxide is listed "choroidal congestion" (a vague condition), but nothing is said about the pupillary disturbances which have frequently been described; carbon tetrachloride is said to cause "amblyopia," although it is a constriction of the peripheral field rather than the central vision which has previously received attention; chloroform is said to reduce intraocular pressure experimentally, scarcely a toxic effect of much general or industrial significance; "dionin" (ethylmorphine hydrochloride U. S. P.), incorrectly spelled "dionene," is said to cause "allergic conjunctivitis," although it is generally considered that this drug (employed medically) more regularly causes conjunctival reaction without necessity of allergy; glycerin is described as causing "iritis," "slight internal congestion" and "slight necrosis (experimental)," although published descriptions of the clinical application of this material indicate that it is fairly innocuous to the human eye; under methyl bromide no mention is made of the recognized local ocular effects; sulfur dioxide is described as causing irritation of the conjunctiva, without note of the much more serious corneal damage which may be produced by it.

Chapter 2 ends with seven pages listing chemical and trade names and manufacturers of various detergents, with no information on ocular effects except a footnote on the first page regarding potential serious "cellular damage" and rapid "hygroscopic" action, which certainly does not present a very accurate picture.

It is regrettable that the air of authoritativeness which is given this misleading collection of material by its uncritical acceptance by the three national ophthalmologic organizations which have sponsored the manual may well lead to a perpetuation of its misconceptions, as well as have medicolegal repercussions. At the least, it will probably encourage persons with keratoconus or iritis from unrelated causes to seek compensation for the imagined effects of a wide variety of chemical exposures.

Chapter 3 presents a brief and reasonable description of first-aid procedure, but again includes the seemingly ill chosen term "hygroscopic action." A sixteen page list of "References for Additional Reading" provides an indiscriminate mixture of good, bad and indifferent source material.

In conclusion, this manual can scarcely be said to fulfil the high expectations one was led to hold for it from a reading of the introduction.

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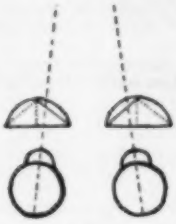

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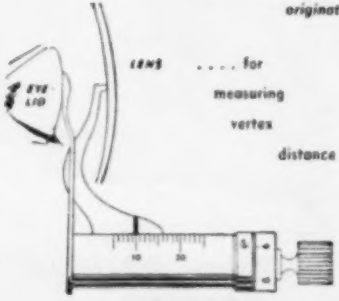

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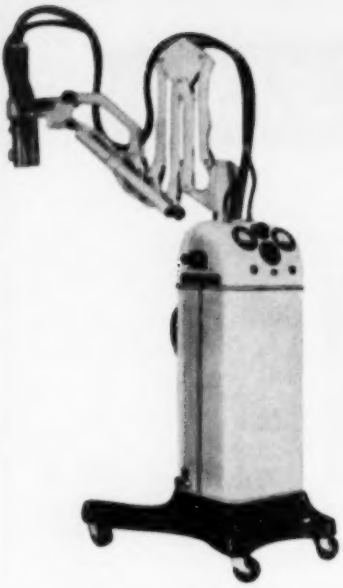

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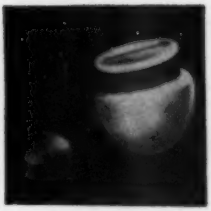

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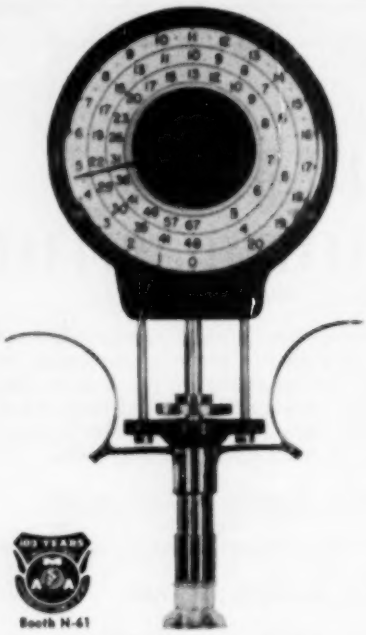

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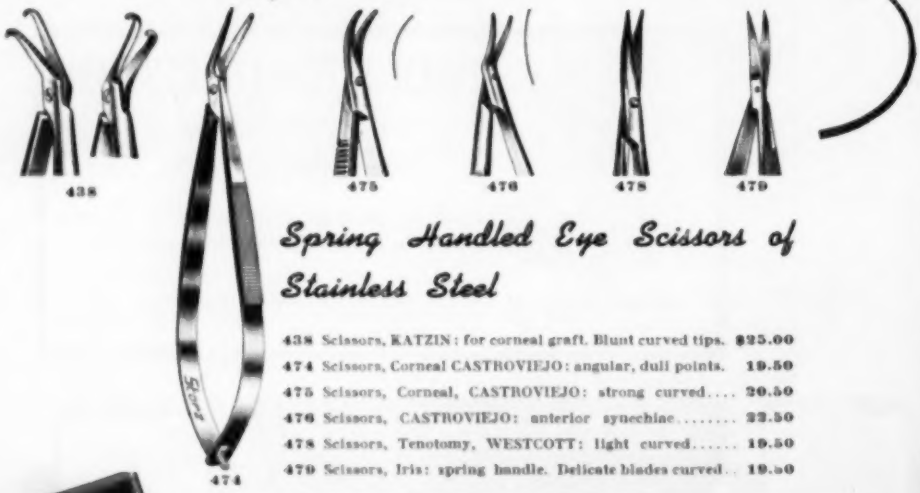

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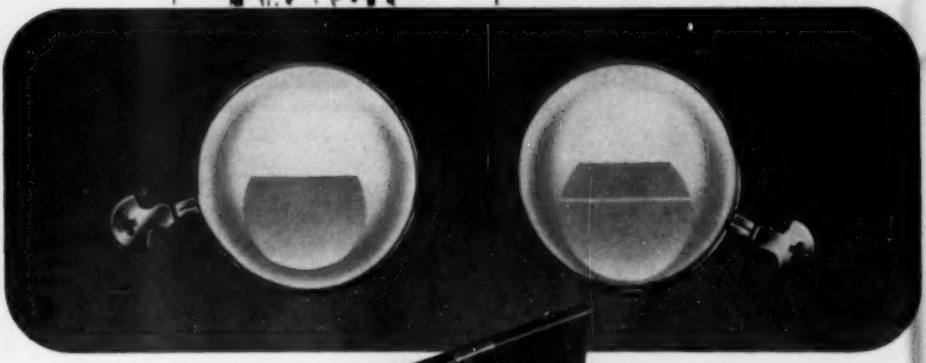

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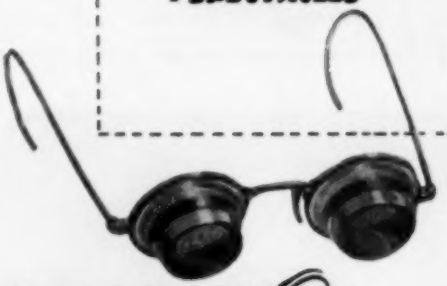

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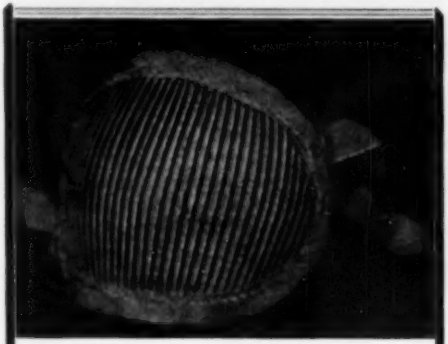

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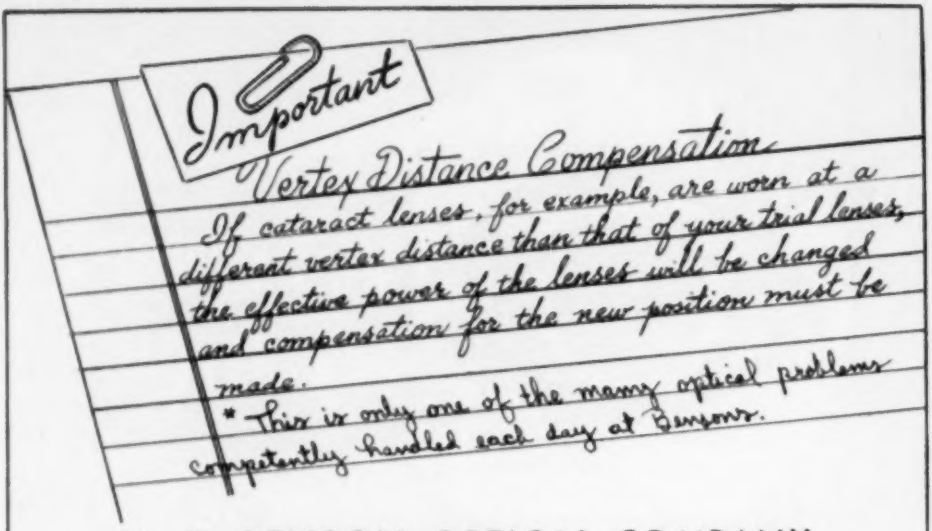
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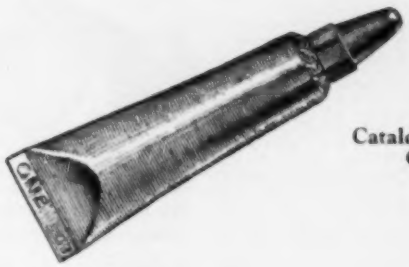

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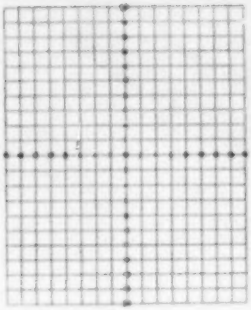

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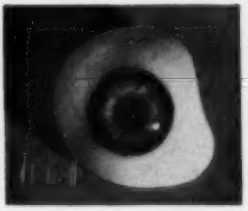

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